

# COMPASSIONATE USE OF INVESTIGATIONAL NEW DRUGS: IS THE CURRENT PROCESS EFFECTIVE?

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## HEARING BEFORE THE COMMITTEE ON GOVERNMENT REFORM HOUSE OF REPRESENTATIVES ONE HUNDRED SEVENTH CONGRESS FIRST SESSION

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## COMPASSIONATE USE OF INVESTIGATIONAL NEW DRUGS: IS THE CURRENT PROCESS EFFECTIVE?

WEDNESDAY, JUNE 20, 2001

HOUSE OF REPRESENTATIVES,  
COMMITTEE ON GOVERNMENT REFORM,  
*Washington, DC.*

The committee met, pursuant to notice, at 1:14 p.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Morella, Horn, Ose, Lewis, Mrs. Jo Ann Davis of Virginia, Platts, Weldon, Duncan, Waxman, Cummings, Kucinich, and Clay.

Staff present: Daniel R. Moll, deputy staff director; James C. Wilson, chief counsel; David A. Kass, deputy counsel and parliamentarian; Mark Corallo, director of communications; S. Elizabeth Clay, Michael Canty, and John Rowe, professional staff members; Robin Butler, office manager; Toni Lightle, legislative assistant; John Sare, deputy chief clerk; Corinne Zaccagnini, systems administrator; Elizabeth Crane, staff assistant; Phil Barnett, minority chief counsel; Kate Anderson and Sarah Despres, minority counsels; Ellen Rayner, minority chief clerk; and Earley Green, minority assistant clerk.

Mr. BURTON. Good afternoon. We will have Members coming and going throughout the hearing, but I want to go ahead and get started because we're already a little behind schedule, so you are going to have to look at my pretty face alone for just a few minutes, but all of this will be on the record for all of the Members.

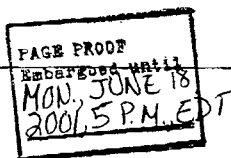
A quorum being present, the Committee on Government Reform will come to order, and I ask unanimous consent that all 11 Members' and witnesses' written and opening statements be included in the record. And without objection, so ordered.

And I ask unanimous consent that all articles, exhibits, and extraneous or tabular material referred to be included in the record. And without objection, so ordered.

To be told that you or someone that you love has a life-threatening illness, shakes you and your family to the very core. The life that you have known is changed forever. Suddenly you are thrown into a maze of medical tests, doctors' appointments, and tough decisionmaking. You and your family become experts in interpreting complex medical jargon and searching the Internet for treatment options. At times you think that the bureaucracy of government pales in comparison to the medical bureaucracy.

This week, a survey published in the “Annals of Internal Medicine” reports that doctors are many times not candid with their terminally ill patients. In 23 percent of the cases in the study, doctors would not give patients a time estimate if asked. In 40 percent of the cases, physicians said they would knowingly give an inaccurate estimate. Three-fourths of those physicians said they would paint a more positive picture than they really believed. Researchers speculated that physicians were afraid that giving bad news would be making a patient’s condition worse.

[The information referred to follows:]



## Prognostic Disclosure to Patients with Cancer near the End of Life

Elizabeth B. Lamont, MD, MS, and Nicholas A. Christakis, MD, PhD, MPH

**Background:** Patients' understanding of their prognosis informs numerous medical and nonmedical decisions, but patients with cancer and their physicians often have disparate prognostic expectations.

**Objective:** To determine whether physician behavior might contribute to the disparity between patients' and physicians' prognostic expectations.

**Design:** Prospective cohort study.

**Setting:** Five hospices in Chicago, Illinois.

**Patients:** 326 patients with cancer.

**Intervention:** Physicians formulated survival estimates and also indicated the survival estimates that they would communicate to their patients if the patients insisted.

**Measurements:** Comparison of the formulated and communicated prognoses.

**Results:** For 300 of 311 evaluable patients (96.5%), physicians were able to formulate prognoses. Physicians reported that they would not communicate any survival estimate 22.7% (95% CI,

17.9% to 27.4%) of the time, would communicate the same survival estimate they formulated 37% (CI, 31.5% to 42.5%) of the time, and would communicate a survival estimate different from the one they formulated 40.3% (CI, 34.8% to 45.9%) of the time. Of the discrepant survival estimates, most (70.2%) were optimistically discrepant. Multivariate analysis revealed that older patients were more likely to receive frank survival estimates, that the most experienced physicians and the physicians who were least confident about their prognoses were more likely to favor no disclosure over frank disclosure, and that female physicians were less likely to favor frank disclosure over pessimistically discrepant disclosure.

**Conclusions:** Physicians reported that even if patients with cancer requested survival estimates, they would provide a frank estimate only 37% of the time and would provide no estimate, a conscious overestimate, or a conscious underestimate most of the time (63%). This pattern may contribute to the observed disparities between physicians' and patients' estimates of survival.

*Ann Intern Med.* 2001;134:1096-1105.

[www.annals.org](http://www.annals.org)

For author affiliations, current addresses, and contributions, see end of text. See editorial comment on pp 1142-1143.

Forty years ago, physicians did not inform most patients with cancer of their diagnoses (1, 2). This practice of nondisclosure is now generally considered out of date, primarily because it may represent physician paternalism that compromises patient autonomy. Indeed, almost all patients with cancer are now informed of their diagnoses (3). Nevertheless, it is not clear how many understand the survival implications, that is, the associated prognosis. Because survival estimates often strongly affect decisions about cancer treatment, especially at the end of life, patients need and often rightly request prognoses when making such decisions (4-7).

Studies that compare physicians' prognostic estimates with those of patients often show a substantial discrepancy between the two. In a study of 100 patients with cancer who were undergoing treatment, Mackillop and colleagues (8) found that one third of those with metastatic cancer thought that they had local or regional disease and were being treated for cure. Similarly, Eidinger and Schapira (9) studied 190 patients being treated for incurable metastatic cancer and found that approximately one third thought that the treatment

would cure them. Weeks and colleagues (10), in their analysis of 917 patients with metastatic colon cancer or advanced non-small-cell lung cancer in the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments, found that patients who had optimistic misperceptions of their prognosis often requested medical therapies that most physicians would consider futile (10). Their study suggests that in patients with terminal cancer, optimistic prognostic estimates may lead to choices of invasive but ineffective medical therapies rather than perhaps more appropriate supportive care.

Previous studies do not clarify the reason for the asymmetry between comparatively optimistic survival estimates made by patients with cancer and the estimates made by their physicians. Do patients misinterpret or deny the poor prognoses that physicians give them? Do physicians think one thing about patients' prognoses but tell the patients something different? Although several factors may be operating simultaneously, some research suggests that at least part of the discrepancy may be due to the generally optimistic prognostic

estimates that physicians give their patients or to omission of prognostic discussions altogether (11).

Our principal objective was to evaluate how often physicians favor communicating frank survival estimates to patients with terminal cancer who request them. An additional objective was to examine how specific patient and physician characteristics are associated with physicians' preferences (that is, their stated intentions) for prognostic communication. To meet these objectives, we interviewed physicians from several specialties who referred their own patients with cancer to hospice terminal care. We asked them to provide us with their most accurate estimate of how long their patients had to live (*formulated prognosis*). We then asked them what they would tell their patients if the patients insisted on obtaining an estimate of how long they had to live (*communicated prognosis*). We compared these two survival estimates and sought to explain discrepancies by evaluating several patient and physician variables in which we had a substantive interest.

#### METHODS

##### Study Sample

We assembled a cohort of all patients with cancer admitted to five outpatient hospice programs in Chicago, Illinois, during 130 consecutive days in winter and spring 1996. We approached all hospices in the Chicago area that admitted more than 200 patients per year, at least 70% from within the Chicago city limits. Six hospices met these criteria, and five agreed to participate; we estimate that most hospice patients in Chicago were captured in our sample. Our research was approved by the institutional review board at each participating hospice and was conducted in accordance with the regulations of these boards. Participating hospices usually notified us about patients on the day of admission. We contacted referring physicians promptly to administer a 4-minute telephone survey about patient prognosis and to collect other information.

A total of 767 patients were referred by 502 physicians during the study period and consented to the study. The five hospices contributed 13%, 14%, 17%, 22%, and 34% of the sample, respectively. Of the 767 patients, 325 did not meet the entry criteria: Two hundred eighty-five had a noncancer diagnosis (an expected percentage based on national data) (12, 13), and 40 had

physicians who were not appropriate participants (that is, they had already responded to several previous cases in the study). Thirty patients died before we were notified of admission. Because they died within a few hours and their physicians' predictions of survival would be meaningless, we did not include them in our cohort. For the remaining 412 eligible patients, we reached 38 physicians (9.2%) after the patient had died (and therefore could not get a meaningful prognostic estimate); we reached 8 physicians (1.9%) before the patient died, but the physician declined to participate; and we failed to reach 40 physicians (9.7%). However, for these 86 patients, we obtained basic physician and patient information and time of death.

We therefore successfully completed surveys with physicians who cared for 326 of the 412 eligible patients (a completion rate of 79.1%). Our analytic sample consists of these 326 patients, who were referred by 258 physicians. When we compared the 326 patients with the 86 excluded patients, we did not find important differences in age, sex, ethnicity, cancer type, or disease duration or in their physicians' sex, practice experience, or specialty. While most participating physicians (83% [214 of 258]) referred only 1 patient, a small number referred more than 1 (range, 2 to 6 patients). The average number of patients per physician was 1.26.

##### Variables and Data Sources

We acquired information about patient age, sex, ethnicity, religion, marital status, cancer diagnosis, and comorbid conditions from the hospices. From the physician telephone survey, we obtained patients' Eastern Cooperative Oncology Group (ECOG) performance status scores (a measure of debilitation that ranges from 0 to 4) (14) and duration of illness. We obtained patients' dates of death from publicly available death registries or from the hospices. As of 30 June 1999, dates of death were known for 96% of the cohort (313 of 326). From the physician telephone survey, we also determined physicians' experience with similar patients and how well they knew the study patients (that is, the duration, recency, and frequency of their contact). From publicly available records, we determined physicians' specialty, years in practice, and board certification.

Our key questions involved 1) an estimate of the patient's prognosis (by asking the physicians to provide



"your best estimate of how long you think this patient has to live") and 2) a comparable statement about what the physician would tell the patient if the patient or family insisted on receiving a specific estimate of survival. We refer to the first prognosis (the estimates of survival given to us by the physicians) as the *formulated prognosis* and the second prognosis (the estimates physicians would give to patients) as the *communicated prognosis*. By design, these two questions were separated by 20 questions that required approximately 2 minutes to answer. Although physicians were not reminded of their formulated prognosis when asked for the communicated prognosis, it was provided if they requested it. Physicians were not asked to explain discrepancies between their formulated and communicated prognoses. We also asked physicians to quantify their confidence in their formulated prognosis as a percentage, from 0% (no confidence) to 100% (complete confidence). The instrument is available from the investigators upon request.

#### Statistical Analysis

We created a multinomial disclosure variable capturing the four possible categories of prognostic disclosure that could result from comparison of the formulated and communicated prognoses. The categories were 1) no disclosure (the physicians formulated a prognosis for the investigators but would not communicate any temporally specific prognosis to the patient), 2) frank disclosure (formulated prognosis was the same as communicated prognosis), 3) optimistically discrepant disclosure (formulated prognosis was shorter than communicated prognosis), and 4) pessimistically discrepant disclosure (formulated prognosis was longer than communicated prognosis). To evaluate associations between the multinomial disclosure variable and categorical and continuous variables, we used chi-square tests and analysis of variance, respectively. We used multinomial logistic regression to model the multivariate effect of patient and physician variables on the intended strategy of prognostic disclosure (15). This type of model describes the relative odds, through conditional odds ratios, of being in one category compared with another (the omitted category, which was frank disclosure). Although 83% of physicians referred only one patient to the cohort, we adjusted our regression model to account for clustering of patients within physicians (16). All analyses were per-

formed by using Stata 6.0 (Stata Corp., College Station, Texas).

Odds ratios may present difficulties when used to characterize relationships, because they may seem to overstate the relative risk when the frequency of an outcome is high. Therefore, we used a variation of a method described elsewhere (17–19) to transform odds ratios into relative risks for selected key comparisons. These relative risks provide an additional, easier to appreciate characterization of the relationship between predictors of interest and the outcome being examined. Such relative risks depend on specified vectors of covariates and would change if different vectors were specified. Therefore, for illustrative purposes, we used the following fixed vector of covariate values, which were determined by their frequency (that is, mean, median, mode), to report the relative risk for intended disclosure behavior in physicians and patients: white female patient, 70 years of age, cancer diagnosis for 32 weeks, ECOG performance status score of 3, 43 weeks of follow-up, male general internist, physician in the lower 75% of practice experience, physician with more than 50% confidence in his or her prediction, physician who had referred fewer than two patients to a hospice in the past quarter, eight previous contacts between the patient-physician pair, and last physical examination 7 days before referral. We then performed selected comparisons of this vector and vectors that differed by one covariate to calculate relative risks. These differing covariate values are as follows: 60-year-old patient, patient with an ECOG performance status score of 2, female physician, physician in the upper quartile of practice experience, physician with less than 50% confidence in his or her prediction, physician with experience treating 13 similar patients, and physician referring two or more patients to a hospice in the previous quarter.

#### Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

#### RESULTS

Table 1 provides descriptive information about the 7 patient and physician sample. The mean age of patients was 69.2 years (range, 19.6 to 98.1 years); 39.6% were

Table 1. Characteristics of 326 Terminally Ill Hospice Patients and Their Physicians

Variable	Complete Sample (n = 326)	Frank Disclosure (n = 111)	No Disclosure (n = 68)	Optimistic Disclosure (n = 85)	Pessimistic Disclosure (n = 36)
<b>Patient characteristics</b>					
Mean age (range), y	69.2 (19.6–98.1)	71.5	69.9	70.0	66.0
Male sex, %	39.6	33.3	44.1	42.4	41.7
Ethnicity, %					
White	51.8	50.4	48.5	58.8	55.6
African American	19.6	23.4	16.2	20.0	19.4
Asian	2.2	1.8	1.5	1.2	2.8
Hispanic	4.3	1.8	5.9	3.5	5.6
Unknown	22.1	22.5	27.9	16.5	16.7
Marital status, %					
Married	43.4	39.6	55.4	35.8	45.7
Single	16.7	16.0	18.5	16.0	17.1
Divorced	10.3	11.3	10.8	6.2	14.3
Widowed	29.6	33.0	15.4	42.0	22.9
Median disease duration, wk	32	32	32	32	32
Median performance status score*	3	3	3	3	2
<b>Physician characteristics†</b>					
Male sex, %	80.2	85.7	74.1	79.1	68.1
Median time in practice, y	17	15	19	18	14
Board certification, %	82.7	83.5	79.3	80.6	73.9
Specialty, %					
General internal medicine and geriatrics	37.0	42.9	33.3	39.4	33.3
Hematology-oncology	23.2	22.0	33.3	18.2	33.3
Other internal medicine	18.1	18.7	15.8	15.1	9.5
Family or general practice	13.8	11.0	10.5	18.2	14.3
Other	7.9	5.5	7.0	9.1	9.5
Median similar patients cared for in the past 12 months, n	3	3	4.5	3	5
Referred >2 patients to hospice in the past quarter, %	33.0	28.6	31.0	35.8	60.9
Median confidence in prediction, %	70.0	75	50	75	75
<b>Patient-physician relationship</b>					
Median duration, wk	43	32	39	78	52
Median contacts in past 3 months, n	8	7	10	7	10
Median time since last physical examination, d	7	7	7	7	7

\* Performance status is measured on the Eastern Cooperative Oncology Group continuous scale of 0 to 4, with 0 indicating normal activity and 4 indicating completely bedbound.

† Because these characteristics are reported at the physician level, the frequencies of disclosure type are given only for the first patient the physician referred in this cohort (n = 358). For these characteristics, the column totals do not apply.

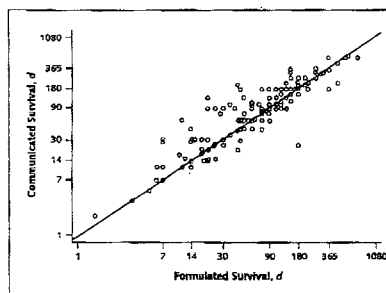
men; and the most frequent principal diagnoses were lung cancer (28.5%), colorectal cancer (10.7%), breast cancer (9.5%), and pancreatic cancer (8.0%). The median ECOG performance status score was 3 (corresponding to >50% of the day spent in bed).

The physicians had been practicing for a median of 17 years (range, 1 to 52 years), and 80.2% were men. Their specialty distributions were general internal medicine and geriatrics (37.0%), medical oncology (23.2%), nononcologic internal medicine subspecialties (18.1%), family practice or general practice (13.8%), and other (for example, surgeons or gynecologists) (7.9%). Although 23.2% of the physicians were medical oncologists, 31.9% of patients were referred by an oncologist,

since physicians could refer more than one patient in the cohort.

Of the 326 patients, 15 were missing data on prognostic disclosure. In 300 of the 311 remaining patients (96.5%), the physicians (n = 241) formulated prognoses and were willing to share them with us. However, physicians reported that in 22.7% (95% CI, 17.9% to 27.4%) of these cases (68 of 300), they would not communicate a temporally specific prognosis if asked by the patients to provide one. In 37% (CI, 31.5% to 42.5%) of these cases (111 of 300), physicians would communicate frank prognoses, and in 40.3% (CI, 34.8% to 45.9%) (121 of 300), they would communicate discrepant prognoses. Among the 121 patients who would have

Figure 1. Relationship between formulated and communicated survival.



The communicated survival and the formulated survival, in days, are shown for a cohort of 232 patients at the time of initiation of home-based hospice care. For the remaining 68 patients in our sample of 300, no prognosis would have been communicated. Not all points are visible because some may overlap precisely. The diagonal line represents frank disclosure. Patients above the diagonal line would receive knowingly overestimated survival information, and patients below the diagonal line would receive knowingly underestimated survival information.

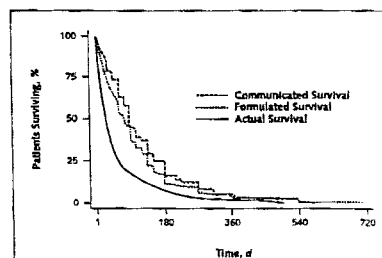
received discrepant prognostic estimates from their physicians, 70.2% (85 of 121) would have received optimistically discrepant prognoses and 29.8% (36 of 121) would have received pessimistically discrepant prognoses. In the 85 patients who would have received optimistically discrepant prognoses, physicians would have overestimated prognosis by a median of 31 days. For 24.7% of these patients (21 of 85), physicians would have overestimated prognosis by at least 60 days (range, 60 to 210 days). Analogously, for the 36 patients who would have received pessimistically discrepant prognoses, physicians would have underestimated prognosis by a median of 19 days.

Overall, the median formulated prognosis was 75 days and the median communicated prognosis (in the 232 patients who would have received one) was 90 days. Thus, physicians would have overstated their formulated prognoses to patients by a factor of 1.2 (90 days/75 days). Figure 1 illustrates the relationship between the formulated and communicated prognoses among the 232 patients for whom physicians would communicate a prognosis. The median actual survival of this sample was 26 days, much shorter than either the formulated or the

communicated prognoses; given this short observed survival, physicians' communicated prognoses would have overstated actual survival by a factor of 3.5 (90 days/26 days). Figure 2 illustrates the relationship between actual survival and the survival patterns based on the physicians' formulated and communicated prognoses.

Bivariate analyses showed that physicians' own estimates of their patients' survival horizons (their formulated prognoses) predicted their communicated prognoses. As shown in Table 2, patients who would have had an optimistically discrepant prognosis communicated to them or no prognosis communicated to them had the shortest anticipated survivals (81 days and 92 days, respectively), those who would have had frank prognoses communicated to them had intermediate anticipated survivals (117 days), and those who would have had pessimistically discrepant prognoses communicated to them had the longest anticipated survivals (128 days) ( $P = 0.04$  for this group of comparisons). In sum, physicians' communication of prognoses was related to the prognoses they formulated. Various patient, physician, and patient-physician relationship variables were important and significant in bivariate analyses and were included in our multivariate model (data not shown). However, we did not include physicians' estimates of patient survival (formulated prognosis) in the multivariate model because it was used to define the out-

Figure 2. Relationship between communicated, formulated, and actual survival.



The differences between actual survival, formulated survival, and communicated survival in 300 terminally ill patients with cancer are shown. The median actual survival was 26 days, the median formulated survival was 75 days, and the median communicated survival was 90 days.

**Table 2. Physicians' Prognostic Disclosure and Estimated Patient Survival\***

Prognostic Communication Category	Mean Formulated Prognosis		Patients <i>n</i>
	<i>d</i>		
Optimistic prognosis	81		85
No disclosure	92		68
Frank prognosis	117		111
Pessimistic prognosis	128		36
Total			300

\* For comparisons between physicians' mean formulated prognosis and their preferences for prognostic communication,  $P = 0.04$ .

come variable (20). Table 1 describes the variation of patient and physician attributes according to disclosure category.

Multinomial logistic regression revealed several factors associated with the four prognostic disclosure categories. Table 3 shows odds ratios (ORs) associated with

patient, physician, and patient-physician relationship variables. With increasing patient age, physicians were more likely to favor frank prognostic disclosure than to favor no disclosure or pessimistically discrepant disclosure. Each 10-year increase in age was associated with a 34% decrease in the relative odds of no disclosure (OR, 0.66 [CI, 0.48 to 0.91]). Based on typical covariate values, this corresponds to a relative risk (RR) of 0.74; hereafter, all reported RRs correspond to the typical covariate values. Each 10-year increase in age was also associated with a 40% decrease in the relative odds of a pessimistically discrepant disclosure (OR, 0.60 [CI, 0.40 to 0.91]; RR, 0.66). As patients' functional status declined, the likelihood of their physicians' favoring frank disclosure rather than pessimistically discrepant disclosure increased; with each incremental increase in numerical ECOG score (representing a decline in performance status), the relative odds that the patient's physician

**Table 3. Association of Patient, Physician, and Patient-Physician Characteristics with Physician Preference for Prognostic Disclosure to Terminally Ill Patients with Cancer\***

Characteristics	No Disclosure		Optimistic Disclosure		Pessimistic Disclosure	
	OR (95% CI)	RR	OR (95% CI)	RR	OR (95% CI)	RR
Patient						
Age (per decade)	0.66 (0.48-0.91)	0.74	0.85 (0.65-1.10)		0.60 (0.40-0.91)	0.66
Male sex	1.85 (0.90-3.80)		1.79 (0.92-3.47)		1.68 (0.55-5.17)	
Disease duration	1.00 (1.00-1.00)		1.00 (1.00-1.00)		1.00 (0.99-1.00)	
Performance status score	1.16 (0.78-1.71)		0.95 (0.68-1.31)		0.58 (0.36-0.92)	0.58
Physician						
Upper quartile of practice experience	2.90 (1.24-6.79)	2.34	1.18 (0.49-2.89)		0.94 (0.25-3.52)	
Female sex	2.96 (1.00-8.74)		2.67 (0.96-7.45)		16.96 (3.85-74.74)	9.00
<50% confidence in prediction	4.42 (1.54-12.65)	3.12	1.26 (0.38-4.16)		1.29 (0.22-7.33)	
Specialty						
Hematology-oncology	1.86 (0.64-5.45)		0.90 (0.36-2.21)		0.63 (0.15-2.72)	
Other internal medicine subspecialty	1.13 (0.38-3.40)		0.68 (0.25-1.86)		1.19 (0.31-4.60)	
Other specialties	1.99 (0.33-12.10)		1.21 (0.28-5.26)		0.63 (0.06-6.98)	
Family practice/general practice	1.04 (0.26-4.18)		2.08 (0.64-6.69)		1.60 (0.24-10.48)	
Cared for similar patients in past 12 months (10-patient increments)	0.98 (0.90-1.08)		0.99 (0.92-1.07)		1.11 (1.01-1.21)	1.11
Referred $\geq 2$ patients to hospice in the past quarter	1.02 (0.42-2.47)		2.14 (1.05-4.34)	1.47	11.04 (3.12-39.14)	7.57
Physician-patient relationship						
Duration (10-week units)	1.01 (0.99-1.02)		1.01 (1.00-1.02)		1.01 (1.00-1.03)	
Number of contacts in past 3 months	0.99 (0.97-1.01)		0.98 (0.96-1.00)		0.97 (0.93-1.00)	
Days since last examination	0.99 (0.97-1.01)		0.99 (0.98-1.00)		0.94 (0.89-0.99)	

\* The dependent variable has four categories: frank disclosure, no disclosure, optimistic disclosure, and pessimistic disclosure. The latter three are compared with the frank disclosure category. All dichotomous variables are coded as 0 = absent and 1 = present. This model also contained dummy variables indicating the hospices and the patient's ethnicity (white, black, other, or unknown), which are not shown. The omitted (reference) category for physician specialty is geriatrics-general internal medicine. Performance status is measured on the Eastern Cooperative Oncology Group (ECOG) continuous scale of 0 to 4, with 0 indicating normal activity and 4 indicating completely bedbound. Relative risk (RR) for associations with significant odds ratios (ORs) were calculated by using the following covariate values: 60-year-old patient, patient with an ECOG performance status score of 2, female physician, physician in the upper quartile of practice experience, physician with less than 50% confidence in his or her prediction, physician with experience treating 13 similar patients, and physician referring two or more patients to hospice in the previous quarter. The baseline vector of covariates for RR determination is as follows: white female patient, 70 years of age, cancer diagnosis for 22 weeks, ECOG performance status score of 3, 43 weeks of follow-up, male general internist physician in the lower 75% of practice experience, physician with more than 50% confidence in his or her prediction and with experience referring three similar patients, physician who had referred fewer than two patients to a hospice in the past quarter, eight previous contacts between the physician-patient pair, and last physical examination 7 days before referral.

would favor pessimistically discrepant disclosure over frank disclosure decreased by 42% (OR, 0.58 [CI, 0.36 to 0.92]; RR, 0.58).

Physicians in the upper quartile of practice experience had nearly three times the odds (OR, 2.90 [CI, 1.24 to 6.79]; RR, 2.34) of favoring no disclosure rather than frank disclosure. Female physicians were more likely to favor pessimistically discrepant disclosure (OR, 16.96 [CI, 3.85 to 74.74]; RR, 9.00) than frank disclosure. As physicians' confidence in their formulated prognoses decreased, their preference for no disclosure increased. For example, physicians whose confidence in their formulated prognoses was less than 50% had more than four times the odds of favoring no disclosure over frank disclosure (OR, 4.42 [CI, 1.54 to 12.65]; RR, 3.12). As physicians' experience with similarly ill patients increased (as measured by the number of recent similar patients or recent hospice referrals), so did their likelihood of favoring some form of nonfrank prognostic disclosure. For example, with each 10 similar patients cared for in the past year, the relative odds of the physician's favoring disclosure of a pessimistically discrepant prognosis increased by 11% (OR, 1.11 [CI, 1.01 to 1.21]; RR, 1.11). Similarly, physicians who had referred two or more patients to hospice programs in the past quarter had 11 times the odds of favoring pessimistically discrepant disclosure (OR, 11.04 [CI, 3.12 to 39.14]; RR, 7.57) and 2.14 (CI, 1.05 to 4.34; RR, 1.47) times the odds of favoring optimistically discrepant disclosure compared with physicians who referred fewer patients.

We evaluated for interactions between physician specialty and patient ethnicity and between physician specialty and physician sex but found no important or significant associations. The interaction terms were not included in the final model.

#### DISCUSSION

We found that physicians favored providing frank survival estimates only 37% of the time to patients with terminal cancer who had been referred for hospice palliative care and who might request such an estimate. Furthermore, physicians favored providing an apparently knowingly inaccurate survival estimate for 40.3% of patients and favored providing no survival estimate for 22.7% of patients. In short, for all of these patients, physicians were able and willing to formulate objective

prognoses, whether accurate or not, but had difficulty communicating them, even to insistent patients. These results suggest that part of the reported discrepancy between patients and physicians on the issue of prognosis may relate to physician nondisclosure or optimistic disclosure. In fact, the overall frequency of discrepant overestimation that we report (28%) is similar to that in previous reports, which found that approximately one third of patients with cancer overestimated their prognoses compared with their physicians (8, 9).

As shown in Figure 2, physicians' predictions contain both conscious and unconscious optimism. The survival prospects that physicians communicate to patients are more optimistic than the survival estimates they formulate, but even the latter are more optimistic than patients' actual survival. This finding regarding the accuracy of formulated prognoses is not the subject of the current study but has been examined in previous research (21–24). Our past work has shown that physicians' formulated prognoses were accurate only 20% of the time in patients referred for hospice palliative care (21). The fact that the formulated and communicated prognoses differ further supports the contention that these are distinct behaviors of physicians caring for patients near the end of life, that both are (independently) prone to error, and that both are relevant to the care patients might receive. These stepwise optimistic prognoses may cause patients to become twice removed from their actual survival. Although a median discrepancy of 15 days between the formulated and communicated prognoses may seem small, we believe that it is important for at least three reasons: 1) It may represent conscious physician behavior; 2) it is relatively large in our study, representing more than half of the true median survival of 26 days; and 3) it occurs in addition to an already overoptimistic formulated prognosis.

What accounts for this lack of support for explicit, frank verbal communication about prognosis to dying patients, even when the patients insist on such information? Several facts seem important. First, we found that physicians with less than 50% confidence in their predictions had four times the odds of favoring no disclosure over frank disclosure compared with more prognostically confident physicians. Some previous research has suggested that physician confidence is not associated with prognostic accuracy itself—that is, that physicians do not accurately perceive their own prognostic abilities

in formulating prognoses (25). Thus, although low confidence does not seem to be associated with prognostic accuracy, it appears to influence the nature of the prognostic communication by decreasing the physician's likelihood of communicating a prognosis to his or her patient.

Second, we found that physicians in the upper quartile of practice experience favor no disclosure over frank disclosure and that physicians with previous experience in the palliative care of dying patients favor disclosure of knowingly inaccurate pessimistic prognoses rather than frank prognoses. Additional research is required to clarify why increasing experience might discourage physicians from frank disclosure. One possibility is that the wisdom born of experience suggests to physicians that it is best not to provide patients with predictions. This seems especially likely given the error in physicians' formulated prognoses, as shown in Figure 2 and elsewhere (21, 22). Experienced physicians may come to believe that since they cannot formulate reliable prognoses, why communicate them? They may also understand their propensity to err optimistically in formulated prognoses and try to correct for it by communicating more pessimistic prognoses to patients. However, older physicians may favor prognostic nondisclosure because of an age-period-cohort effect; the older physicians in our sample received their medical education and training in the 1950s and 1960s, a time when nondisclosure of cancer diagnoses was common, and this may explain their current disclosure styles (26).

Our study has several limitations. First, the assumption that physicians favored providing their patients with "knowingly inaccurate" prognoses when the formulated and communicated prognoses differed may be incorrect. The physicians may have forgotten the estimate given to the investigators earlier in the questionnaire, and the difference between what they told the investigators and what they would favor telling the patients may have been unintentional. The short interval between the two queries and the asymmetrical pattern of the discrepancies (optimistic communication substantially predominated) suggest otherwise, however. Second, our categorization of physician preferences for prognostic disclosure is based on a hypothetical situation in which a patient insists on receiving a temporally specific prognostic estimate; therefore, it may not reflect true clinical practice. Third, because the patients in our

sample had already been referred to hospice palliative care, an event that has prognostic implications, it is not known whether our results are generalizable to other populations. However, if physicians infrequently provide frank disclosure to hospice patients with cancer who request it, they may be even less likely to provide it to inquiring nonhospice patients, with or without cancer. Finally, although our response rate (79.1%) is higher than that of typical physician surveys (27), it is still less than 100%. This contributes to the potential for nonresponse bias and suggests that caution should be used when generalizing our results.

Our study has several implications. Previous studies have shown that patients usually want prognoses (4–6) and that they need them in order to make decisions that are most in keeping with their true preferences for end-of-life care (28, 29). Insofar as patients want and need prognoses, and insofar as the medical profession is committed to respecting patient autonomy, frank communication about prognosis between physicians and inquiring patients seems optimal. Clearly, however, communication of bad news needs to be handled tactfully and respectfully, and resources are available to guide physicians in this challenge (11, 30, 31). Our study should not be taken to support the deplorable practice of "truth dumping." Rather, we believe that physicians need to face the difficulties involved when seriously ill patients insist on temporally specific prognoses. Armed with such information, patients might be better able to plan for, and achieve, the kind of "good death" most Americans say they want (32, 33).

In general, we found that the propensity to avoid frank disclosure was relatively homogeneously distributed among patients and physicians. That is, most types of physicians tend to avoid frank disclosure for most types of patients with cancer. This has implications for the way we train physicians to break bad news about serious illness, since it suggests that no specific type of physician is prone to the behavior we have described and no specific clinical situation is most problematic.

However, if this type of enhanced communication between physicians and patients regarding prognoses at the end of life is to be of real use to patients, the medical profession will clearly need to improve the science of prognostication, allowing fewer errors in the formulated prognosis. What good does it do to encourage physicians to communicate information that is, after all, in-

accurate? Several methods are available for enhancing the accuracy of formulated prognoses, including using statistical algorithms, averaging prognoses made by several physicians, and consulting more experienced colleagues or textbooks (21, 34, 35).

Studies show that although patients with cancer want their physicians to provide detailed prognoses, they also want their physicians to give them good news and to be optimistic about their illnesses (4, 11, 36). The paucity of frank disclosure seen in our study, for patients in whom prognostic communication should theoretically present relatively few challenges, may indicate the impossibility of this task. Nevertheless, physicians report that they do not support frank disclosure for most patients with terminal cancer who request specific prognoses.

From University of Chicago Medical Center, Chicago, Illinois.

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**Requests for Single Reprints:** Nicholas A. Christakis, MD, PhD, MPH, University of Chicago Medical Center, 5841 South Maryland Avenue, MC 2007, Chicago, IL 60637; e-mail, nchrista@medicine.bsd.uchicago.edu.

**Current Author Addresses:** Drs. Lamont and Christakis: University of Chicago Medical Center, 5841 South Maryland Avenue, MC 2007, Chicago, IL 60637.

**Author Contributions:** Conception and design: N.A. Christakis. Analysis and interpretation of the data: E.B. Lamont, N.A. Christakis. Drafting the article: E.B. Lamont, N.A. Christakis. Critical revision of the article for important intellectual content: E.B. Lamont, N.A. Christakis. Final approval of the article: E.B. Lamont, N.A. Christakis. Provision of study materials or patients: N.A. Christakis. Statistical expertise: E.B. Lamont, N.A. Christakis. Obtaining of funding: E.B. Lamont, N.A. Christakis. Administrative, technical, or logistic support: N.A. Christakis. Collection and assembly of data: E.B. Lamont, N.A. Christakis.

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I am very much against the inclusion of any cigarettes in the ration. Apart from the very real objection to the continuous coughing and expectorating they cause, they do, in fact, give rise to the very evils they are supposed to alleviate. They are supposed to soothe the nerves, and one cigarette undoubtedly has this effect, but the habit of smoking promotes irritability and makes its victim unable to do without it. Since, in campaigns of this nature, men cannot depend on a constant supply of cigarettes they are ill advised to pursue the habit. From my own experience the habit can be abandoned and not missed a month afterwards . . . Doctors' recommendations on this subject are biased as they are all inveterate smokers.

John Bierman and Colin Smith  
*Fire in the Night: Wingate of Burma, Ethiopia and Zion*  
New York: Random House; 1999:261

Submitted by:  
A.M. Clarfield, MD, FRCP  
Sara Herzog Hospital  
Jerusalem, Israel 91351

Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.—The Editor



*Summaries for Patients* are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Prognostic Disclosure to Patients with Cancer near the End of Life." It is in the 19 June 2001 issue of *Annals of Internal Medicine* (volume 134, pages 1096-1105). The authors are EB Lamont and NA Christakis.

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MON, JUNE 18  
2001, 5 P.M. EDT

## How Willing Are Doctors To Give Patients with Terminal Cancer Accurate Information about Their Chances of Survival?

### What is the problem and what is known about it so far?

Patients with terminal or end-stage cancer sometimes do not understand their actual chances of survival. This misunderstanding can affect their decisions regarding treatments and end-of-life care. Patients may misunderstand their survival chances for several reasons. For example, some patients may continue to believe they will be cured despite being told otherwise. Families may sometimes contribute to patients' misunderstandings by hiding or downplaying negative information. Moreover, doctors may not discuss survival chances with patients, or they may give patients inaccurate information. Few studies have investigated doctors' willingness to give terminally ill patients information about their chances of survival.

### Why did the researchers do this particular study?

To find out how often physicians would willingly give patients with terminal cancer their best estimates of how long the patients are likely to survive.

### Who was studied?

The study included 258 physicians who cared for 326 patients with terminal cancer. Physicians included generalists (internists and family practitioners), oncologists (specialists in cancer), gynecologists, and surgeons. Eighty percent of the physicians were men.

### How was the study done?

The researchers asked the physicians to estimate the chances of survival for each of their 326 patients. The physicians were also asked what they would tell these patients if either the patient or a family member insisted on receiving a specific estimate of survival. The researchers then compared the physicians' estimates of survival with what the physicians said they would actually tell their patients.

### What did the researchers find?

Physicians said they would withhold information altogether about survival estimates from 23% of their patients. They said they would tell 37% of their patients their actual survival estimates and would give survival estimates different from the ones they actually estimated to 40% of their patients. In these latter instances, physicians most often said they would give patients estimates that were longer than their actual estimates. Physicians said they would more often have frank discussions with older than younger patients. Female physicians and physicians who had treated many patients with terminal cancer were least likely to favor frank discussions with their patients.

### What were the limitations of the study?

This study was based on what physicians said they would do rather than what they actually did; whether their thoughts of what they would do match their actual practice is not known. Also, it is difficult for physicians to make exact estimates of how long individual patients will survive.

### What are the implications of the study?

Physicians who care for patients with terminal cancer say that they would often not provide such patients their best estimates of survival. Failing to share that information may contribute to patients' misunderstanding about their chances of survival and may affect their decisions about cancer treatment.

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## EDITORIAL

## Truth in the Most Optimistic Way

While I was in residency at the Mayo Clinic, my oncology attending arrived for rounds one day with a sheepish grin on his face. It was June 3rd, you see, and for the 7th straight year a former patient of his had called him and angrily exclaimed, "I am still alive, you idiot!" before slamming down the telephone. Seven and a half years ago, the oncologist had given the man 6 months to live.

Since then, I have stopped giving patients specific predictions about their life expectancies. I recognize that patients need to know their prognoses to make treatment decisions and plan their affairs. However, I have found that relatively nonspecific prognoses are sufficient. I might say, "I cannot predict the future, but in my experience, patients with your illness typically live a matter of months, not years," or "Many people in your condition will live for only a matter of weeks, but some live significantly longer. I do not know what your fate will be." In these conversations, I discuss concrete treatment goals with patients. I do not hesitate to say when I think the goal should shift from cure to palliation. When things are grim, I suggest that it is time to visit with friends and family because "it is better to be safe than sorry." I give enough prognostic information to help patients make decisions, but I avoid using numerical wording that suggests I have a prognostic crystal ball.

In this issue, Lamont and Christakis (1) report the results of a survey of physicians who had referred patients with cancer to local hospices. They asked each physician to estimate how long his or her patient would live. In a later question, they asked physicians what prognostic information they would communicate if patients insisted on receiving such information. They found that almost one quarter of physicians would not communicate a temporally specific prognosis, 37% would communicate the same prognosis that they had estimated, 28% would provide an optimistic prognosis (a longer survival than predicted), and a small number would provide a pessimistic prognosis.

I do not know where my practice style would fit in this classification scheme. On the basis of conversations I have had with other physicians since reading Lamont and Christakis's article, my communication style is relatively common. The physicians I spoke with, an admittedly unscientific sample, said that they were reluctant

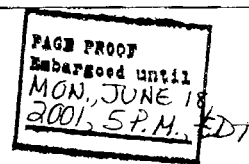
to provide *specific* predictions to patients. Their reluctance is based not on a desire to withhold information from patients but on uncertainty about their predicting abilities. When I mentioned that the physicians in Lamont and Christakis's study were a median of 70% confident in their prognoses, most of my colleagues replied that even if they were 70% confident (whatever that would mean), they would still be too uncertain to provide specific numerical prognoses to patients.

What prognostic information should physicians communicate to patients with terminal illnesses? When I discussed Lamont and Christakis's research with a taxi driver, he had a simple prescription for how he would want physicians to communicate with him if he were to develop a terminal illness: "Tell me the truth in the most optimistic way."

But what is the truth here? The disparity that Lamont and Christakis found between physicians' formulated prognoses and communicated prognoses suggests that some of these physicians were being less than forthcoming by, for example, refusing to provide specific prognoses. Lamont and Christakis point out that such refusals were especially common among older physicians, who had trained in an era when patients were often left in the dark not only about their prognoses but also about their diagnoses (2). Perhaps these physicians represent the last vestige of paternalism.

Yet I am not so sure that physicians who refused to provide specific prognoses were withholding information from their patients. To encourage physicians to formulate prognoses, Lamont and Christakis asked the following: "For the next question, please again assume the patient has the most *typical* course and that *the patient receives the type of care after referral to the hospice that you expect* [their emphasis]. We recognize that it is very hard to make such predictions, but we would be grateful for your best estimate of how long you think that this patient has to live."

This wording encourages physicians to take a stab at formulating a prognosis for a *typical* patient who receives a *specific* kind of care. Given these assumptions, physicians may have been able to formulate prognoses. But how confident were they that their specific patients would follow this course and receive this care? Physi-



cians' reluctance to give specific predictions may result from their awareness that not all patients are typical.

What about the physicians who communicated optimistic prognoses to their patients? Were they being less than forthcoming? Some of these physicians may have stretched the truth beyond its optimistic limits, but such stretching was probably well intentioned. Patients want to hear that there is hope. And, just as important, physicians want to communicate hope to their patients; communicating hope can improve patients' prognoses. Mildly but unrealistically positive beliefs can improve outcomes in patients with chronic or terminal diseases (3). For example, a late-1980s study of patients with AIDS found that those who stated that they "refused to believe that this problem has happened" lived 9 months longer than those who indicated that they "tried to accept what might happen" (4). Moreover, unrealistically optimistic views have been shown to improve quality of life (5-7). Providing optimistic prognoses might even improve physicians' spirits. This may be especially important for oncologists, who regularly deal with dying patients and may therefore need to find ways to hope that patients will do better than expected.

Perhaps the most puzzling group of physicians is the small number who would have chosen to provide pessimistic prognoses. Were they less than forthcoming? Drawing on my clinical experience, I would guess that many physicians base their communication on the way patients react to their prognoses. When patients are "too pessimistic" about their illnesses, physicians emphasize hope in order to lift their spirits. When patients are "too optimistic," physicians make sure patients understand the gravity of their situations. The small group of physicians in this study who said they would provide pessimistic prognoses probably did so because of how their specific patients had interpreted their illnesses so far.

Before judging the physicians in Lamont and Christakis's study, we should remember that all had recently referred their patients to local hospices. Thus, it is likely that the major goals of prognostic communication had already been achieved. Since the patients were receiving hospice care, they knew that they had terminal illnesses, had chosen to abandon any attempts at miraculous cures, and had elected a course of palliative care. Such decisions would have been unlikely if physicians had been systematically misleading them about prognosis.

Lamont and Christakis's study deserves widespread attention and discussion. It also deserves to be followed with further research that clarifies physicians' reasons for communicating or not communicating specific prognostic information to terminally ill patients. Prognostication will never be an exact science. The prognostic information we communicate to patients should be vague enough to include the truth—"usually weeks or months"—and specific enough to help people plan their lives and deaths. Numerically specific prognostic communication can be the enemy of hope. The truth we communicate to patients should help them prepare for the worst while allowing them to hope for the best.

Peter A. Ubel, MD

Ann Arbor Veterans Affairs Medical Center  
University of Michigan Health System  
Ann Arbor, MI 48109-0429

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**Current Author Address:** Peter A. Ubel, MD, University of Michigan Health System, 300 North Ingalls, Room 7C27, Ann Arbor, MI 48109-0429; e-mail, paubel@umich.edu.

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Mr. BURTON. This is a very touchy issue. Patients should be told the truth, in a compassionate, and as much as possible, in a positive way when asked questions about their situation. I believe that doctors can deliver accurate information with compassion. I also believe that your doctor should also be your strongest advocate. He or she should offer information on all treatment options available—standard treatments, alternative therapies, and experimental treatments. Unfortunately, this does not happen. Many times doctors are not aware of the latest treatment options or do not take the time to be informed. This is not how our health care system should function.

The decision on what course of action to take should always be the patient's. If the standard therapies fail, they may seek access to experimental treatments. Increasingly, individuals will seek an integrative approach, combining conventional and complementary therapies in an effort to treat the whole person, not just the disease or the tumor. A patient's desire to try an integrated approach should be respected and allowed.

I repeat—the decision on what course of action to take is the patient's. After given the facts, if someone with a life-threatening or terminal illness wants to seek treatments that may offer a cure or a slowdown in the progression of disease, then Federal agencies and red tape should not stand in their way.

Today's hearing will focus on compassionate access to experimental drugs. Science dictates a gradual process of information gathering that often takes 12 to 15 years from inception to product approval. When research moves to the point of human subject involvement, an investigational new drug [IND] application is submitted to the Food and Drug Administration. There is careful review of the preliminary safety data and protocol designed before the trials can move forward, and that is as it should be.

Clinical trials are carefully designed to collect information about product safety and efficacy. Access to experimental treatments through clinical trials is the best route. However, not all cancer and AIDS patients fit protocol designs. Their disease may be more advanced, they may be the wrong age, or have had too many rounds of chemotherapy or radiation. Whenever feasible, when a patient is not able to participate in a clinical trial, they should not be excluded from access if there is some hope that a drug may save or extend their life.

We are going to hear today from Dr. Robert Temple of the FDA, that the term the public uses, "compassionate use," is actually an umbrella term for a myriad of mechanisms available to provide patients access to drugs outside of clinical trials.

To an individual who needs access to an experimental drug, they do not really care if it is through a special exemption IND, a treatment IND, or a single-patient IND. They just want access to the treatment. They want to live. They want a chance to live.

In the past few weeks we have seen a media focus on the plight of individuals who sought access to experimental treatments. Frank Burroughs' 21-year-old daughter, Abigail, lost her battle with cancer just 11 days ago. And he has our sympathy, as does his whole family. He will share their story of trying to access ex-

perimental drugs that Abigail's oncologist thought would be helpful.

Fred Santino's wife, Ruth-Ann, fought a 2½ year battle with colorectal cancer. She withstood numerous surgeries and chemotherapy treatments, but continued to have progression of her disease. She sought access to experimental treatments. One option she sought was C225. This product is being developed by ImClone Systems, had been shown in phase II studies to be effective in treating colon cancer with metastases. She was not able to access the treatment, and she died in May.

And one of the things that concerns me about clinical trials, which are very, very important, is whether or not either financial interests or statistical data being gathered in the clinical trials is the reason that they do not give people compassionate use of some of these drugs. And if that is the case, one of the things that I would like to suggest today is that the clinical trial be walled off completely, so that no adverse information from a compassionate use be included or have any impact on the clinical trial. And the reason I say that is I understand the financial problems a small company would have to be involved in if this information was put into the clinical trials. It could destroy the company, it could cause the clinical trial to be skewed, it could be a real problem.

But on the other hand, if it is being effective and being shown to be effective, and that leaks out into the public domain, as it has in the C225 case, you have people out there who may be without hope; their doctor may have said, "You are going to die", and they want to have at least a chance to survive. And so compassionate use of that drug should be considered for that individual.

And if the other concerns are viable concerns, then the clinical trial should be walled off and we should find a way to give hope to the person who's dying and have a chance to get that treatment.

And I will tell you that in my life, I have known people in the medical profession, very highly regarded people, people in our government who were the heads of major agencies that deal with our health care, who were against using treatments outside of conventional medicine. And yet when their loved one, their wife, became terminally ill, they tried everything. They went out of the country, they did everything, because it is different when you are talking about the masses of people and people who are suffering from a disease that is incurable, when there is a new drug that may save their life, and when it is in your family, when your wife or your daughter or your son is terminally ill with a disease and there is no hope except that long, long bomb that we are talking about, that you might throw in a football game, with a new drug that might save their life.

And so that is why I think we ought to look at walling off clinical trials from the compassionate use if that is what is necessary to give every person every chance to survive.

What these two families learned, the ones I just mentioned, is that many companies do not have clear guidelines on when compassionate access is going to be provided. Some companies such as AstraZeneca have clearly defined programs that are posted on their Web site. AstraZeneca, one of the largest pharmaceutical companies in the world, developed an expanded access protocol for

IRESSA, a lung cancer treatment they have in development. They set this program up with a third party, the National Organization for Rare Disorders.

ImClone, a relatively small company, had no established program, and when researchers started talking about their positive effects, they were overwhelmed with requests, and as a result, have closed their compassionate access program. And we understand the problems they are facing. And we are not here to be judgmental today. We are here to try to find some answers for people who are terminally ill.

Dr. Waksal, the president of ImClone, will share their story of the challenges today.

We will also hear from one of the fortunate ones, a lady named Shannon Kellum. Shannon, at age 28, was diagnosed with colon cancer. She was the first colon cancer patient to try C225, through compassionate access. She lucked out because her physician had done some of the preclinical research on C225 and was able to use that knowledge to convince ImClone that she should have access to the treatment.

Doug Baxter's 16-year-old son, David, was recently diagnosed with colon cancer. He will tell us about their ongoing struggle to access experimental treatments and save David's life.

David Barr is living with AIDS. He will share his perspectives on how the AIDS community worked together to force the FDA's hand on expanding access to experimental treatments.

How can we improve compassionate access to experimental drugs? How can we give hope to people? And hope is a very strong ingredient in survival. How can we give hope to people who have been told, in effect, that they are terminally ill? Does the FDA need to allow companies to manufacture a larger supply of the experimental product during the developmental process? Is money an issue? Are the reporting requirements on efficacy data outside clinical trials a barrier? And once again, that is why I suggested that maybe you wall off the clinical trial.

There are many people who have had an opinion on this topic. We received written testimony from the National Breast Cancer Coalition, and I ask that it be included in the hearing record. And without objection, so ordered.

[The information referred to follows:]

# NBCC

NATIONAL BREAST CANCER COALITION

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*grassroots advocacy in action*

June 19, 2001

Chairman Dan Burton  
Committee on Government Reform  
2157 Rayburn House Office Building  
Washington, DC 20515

Dear Chairman Burton:

On behalf of the National Breast Cancer Coalition (NBCC) and the 3 million women living with breast cancer, I thank you for holding a hearing on compassionate use of investigational new drugs (INDs) for terminally ill patients. NBCC believes that a policy supporting compassionate use of investigational new drugs for individuals will weaken the move towards more and better research, expanded clinical trials, and access to health care for all Americans.

As you are aware, NBCC, a grassroots advocacy organization whose sole purpose is to eradicate breast cancer through action and advocacy, is now more than 600 organizations and 60,000 individual members strong. The Coalition's main goals are to increase federal funding for breast cancer research and collaborate with the scientific community to implement new models of research; improve access to high quality health care and clinical trials for all women; and expand the influence of breast cancer advocates in all aspects of the breast cancer decision making process.

Since NBCC's beginning nearly ten years ago the concept of evidence-based medicine has been fundamental to the Coalition. We want to know what works for women with and at risk of breast cancer, and we want all women to have access to what works. Women with breast cancer should not be given false hope by treatments that are unproven. Interventions must be based on the best possible science available, and the best way to achieve that is through well-designed clinical trials. We continue to help develop policies to increase the number of quality clinical trials, and bring the perspective of breast cancer advocates to the design of trials.

There are all too few truly effective treatments for most types of cancer. While the public is inundated with information about cancer "breakthroughs" and news of promising new drugs, the reality is that most drugs result in incremental improvement. The research process seems agonizingly slow for those who have run out of treatment options. Pharmaceutical companies, scientists and the media each bear responsibility for creating unreasonable expectations about unproven drugs. This has created a climate where many patients mistakenly believe that access to an investigational drug is their last hope, when most often it is a false hope.

Public policy should discourage access to investigational drugs outside of clinical trials. The Coalition believes that single patient INDs should not be granted. Any access to investigational drugs outside of a clinical trial should be in the context of expanded access protocols only, in which distribution of the investigational therapy is fair and data is captured that will add to the scientific base of knowledge about the intervention. Expanded access should not be the norm, rather a protocol may be allowed in particular circumstances and only for individuals who do not meet the eligibility requirements of a clinical trial. If

1707 L Street, NW, Suite 1060, Washington, DC 20036 phone: (202) 296-7477 fax: (202) 265-6854  
[www.stopbreastcancer.org](http://www.stopbreastcancer.org)

an expanded access program is allowed, access to the drug must be fairly and blindly allocated and all individuals who apply to the program must be followed, and their data reported to the trial sponsor. Expanded access should not be allowed until there is safety data available from a completed phase II trial of the drug, including data that provides some basis for determining that the drug may be efficacious.

It is compelling to argue that there is little harm in making an investigational therapy available to a seriously ill individual for whom there is no effective therapy, if someone is willing to pay for it. This argument does not hold upon scrutiny. To follow this to its logical conclusion completely undermines research and the concept of evidence based care. Where would the line be drawn? It would mean that any individual should have access to any drug, as long as she is willing to pay for it.

Investigational treatments made available outside of clinical trials have the potential to undermine the clinical trials system. There is little incentive for a patient to participate in a clinical trial if she can obtain the investigational drug outside of the trial. This makes trial accrual difficult, and may significantly undermine the ability of the investigators to determine the efficacy and safety of the intervention. (That was certainly the case with bone marrow transplant for breast cancer - because it was so widely available outside of clinical trials it was extremely difficult to accrue patients to trials, and it took many years longer than it should have to learn that the high-risk and expensive procedure provides no benefit to women with breast cancer.)

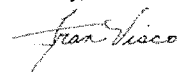
Investigational treatments are by definition unproven; even the most promising data in earlier stages of trials often do not hold up. Further, there may be significant safety issues that do not emerge until well into a phase III trial. For example, the cardiotoxicity of Herceptin was not apparent in the phase II data, but emerged in the much larger phase III trial.

Single patient INDs raise serious issues of fairness. Patients who have access to them are usually very knowledgeable and well connected. They have access to physicians who have the ability to develop a protocol for them, and are willing and able to implement it. This is not the case for many if not most women with breast cancer. Resources devoted to fighting breast cancer should be allocated fairly, based on the best evidence available. The off-trial process involves a great deal of time and expense for clinicians, regulators and investigators, with very little likelihood of benefit to the patient, or to accumulation of knowledge about the intervention in question, that would benefit all.

We recognize this is an extremely difficult issue. We all want to save lives. We must work together to develop the right public policy that will achieve that goal. This policy must move towards more and better research, expanded clinical trials, and access to health care for all Americans. The National Breast Cancer Coalition is committed to a public policy agenda that will help all women with breast cancer and those at risk. We believe that a policy supporting single patient INDs will undermine those efforts.

Thank you for the opportunity to comment on this important issue.

Sincerely,



Fran Visco  
President

cc: Members of the Government Reform Committee



Mr. BURTON. We will keep the hearing record open until July 6 for those who would like to submit written testimony, and we will continue seeking input from organizations, manufacturers and families, about how to improve access to experimental treatments. Whatever it takes, regulatory or legislative changes, or better information sharing, we as the Congress cannot ignore the needs of those with life-threatening illnesses. And I speak with some personal knowledge of this.

[The prepared statement of Hon. Dan Burton follows:]

Opening Statement  
of  
Chairman Dan Burton  
Government Reform Committee

Hearing

“Compassionate Use INDs –  
Is the Current Process Effective?”

June 20, 2001  
1:00 pm  
2154 Rayburn House Office Building  
Washington, DC

To be told that you or someone you love has a life-threatening illness shakes you to your very core. The life you have known is changed forever. Suddenly you are thrown into a maze of medical tests, doctor's appointments, and decision-making. You and your family become experts in interpreting complex medical jargon and searching the Internet for treatment options. At times you think that the bureaucracy of government pales in comparison to the medical bureaucracy.

This week, a survey published in the *Annals of Internal Medicine* reports that doctors are not candid with their terminally ill patients. In twenty-three percent of the cases in the study, doctors would not give patients a time estimate if asked. In forty percent of the cases, physicians said they would knowingly give an inaccurate estimate. Three-fourths of those physicians said they would paint a more positive picture than they really believed. Researchers speculated that physicians were afraid that giving bad news would make a patient's condition worse.

This is a complex dilemma. Patients should be told the truth when they ask questions. I believe that doctors can deliver accurate information with compassion. I also believe that your doctor should also be your strongest advocate. He or she should offer information on all treatment options available – standard treatments, alternative therapies, and experimental treatments. Unfortunately, this does not happen. All too often doctors are not aware of the latest treatment options or do not take the time to be informed. This is not how our health care system should function.

The decision on what course of action to take should always be the patient's. If the standard therapies fail, they may seek access to experimental treatments. Increasingly, individuals will seek an integrative approach – combining conventional and complementary therapies in an effort to treat the whole person not just the disease or tumor. A patient's desire to try an integrated approach should be respected and allowed.

I repeat -- the decision on what course of action to take is the patient's. If someone with a life-threatening or terminal illness wants to seek treatments that may offer cure or a slow down in the progression of disease, federal agencies and red tape should not stand in their way.

Today's hearing will focus on compassionate access to experimental drugs. Science dictates a gradual process of information gathering that often takes twelve to fifteen years from inception to product approval. When research moves to the point of human subject involvement, an Investigational New Drug (IND) application is submitted to the Food and Drug Administration (FDA). There is careful review of the preliminary safety data and protocol design before the trials can move forward.

Clinical Trials are carefully designed to collect information about product safety and efficacy. Access to experimental treatments through clinical trials is the best route. However, not all cancer and AIDS patients fit protocol designs. Their disease may be more advanced, they may be the wrong age, or have had too many rounds of chemotherapy or radiation. Whenever feasible, when a patient is not able to participate in a clinical trial, they should not be excluded

from access if there is some hope that a drug may save or extend their life.

We are going to hear today from Dr. Robert Temple of the FDA that the term the public uses – “compassionate use” is actually an umbrella term for a myriad of mechanisms available to provide patients access to drugs outside clinical trials.

To an individual who needs access to an experimental drug, they don’t really care if it is through a special exemption IND, a treatment IND, or a single patient IND. They just want access to the treatment. They just want the chance to live.

In the past few weeks, we have seen a media focus on the plight of individuals who sought access to experimental treatments. Frank Burrows’ twenty-one year old daughter Abigail lost her battle with cancer just eleven days ago. He will share their story of trying to access experimental drugs that Abigail’s oncologist thought would be helpful.

Fred Santino’s wife, Ruth-Ann, fought a two and a half year battle with colorectal cancer. She withstood numerous surgeries and chemotherapy treatments, but continued to have progression of her disease. She sought access to experimental treatments. One option she sought was C225. This product which is being developed by ImClone Systems, had been shown in Phase Two studies to be effective in treating colon cancer with metastases. She was not able to access the treatment, and died in May.

What these two families learned is that many companies do not have clear guidelines on when compassionate access will be provided. Some companies, such as AstraZeneca, have clearly defined programs that are posted on their website. AstraZeneca, one of the largest pharmaceutical companies in the world, developed an expanded access protocol for IRESSA, a lung cancer treatment they have in development. They set this program up with a third party – the National Organization for Rare Disorders.

ImClone, a relatively small company, had no established program and when researchers started talking about their positive effects, they were overwhelmed with requests and as a result have closed their compassionate access program. Dr. Waksal, the President of ImClone will share their story of the challenges today. We will also hear from one of the fortunate ones – Shannon Kellum. Shannon, at age 28 was diagnosed with colon cancer. She was the first colon cancer patient to try C225 – through compassionate access. She lucked out because her physician had done some of the pre-clinical research on C225 and was able to use that knowledge to convince ImClone that she should have access to the treatment.

Doug Baxter's 16 year-old son, David, was recently diagnosed with colon cancer. He will tell us about their ongoing struggle to access experimental treatments and save David's life.

David Barr is living with AIDS. He will share his perspectives on how the AIDS community worked together to force the FDA's hand on expanding access to experimental treatments.

How can we improve compassionate access to experimental drugs? Does the FDA need to allow companies to manufacture a larger supply of the experimental product during the development process? Is money an issue? Are the reporting requirements on efficacy data outside clinical trials a barrier?

There are many people who have an opinion on this topic. We have received written testimony from the National Breast Cancer Coalition. I ask that it be included in the hearing record. We will keep the hearing record open until July 6 for those who would like to submit written testimony. We will continue seeking input from organizations, manufacturers, and families about how to improve access to experimental treatments. Whatever it takes, regulatory or legislative changes, or better information sharing, we as a Congress cannot ignore the needs of those with life-threatening illnesses.

I now recognize the ranking minority member, Mr. Waxman for his opening statement.

Mr. BURTON. I now recognize the ranking minority member, Mr. Waxman.

Mr. WAXMAN. Thank you very much, Mr. Chairman, and I want to thank you for holding this hearing. This is an important hearing, and I think we have got a record to make and a job to do.

Today we are going to hear about personal experiences that no one should ever have to experience. We are going to hear about people who have fatal cancers and no treatment options until they hear about a promising treatment in the clinical trial process. They appeal to the manufacturer for compassionate use of a drug, and they are denied. They know that other people are getting the drug on a compassionate use basis, but they cannot. We will hear about their bravery as they faced this situation, not giving up and continuing to fight for access to this treatment until the end.

We will hear from the CEO of a company that makes this new drug. He will tell us about the promise of this drug and the progress of the clinical trials. He will tell us that when the promise of the drug became known, 10,000 people applied to use the drug under a compassionate use IND. However, this is a difficult drug to make, and because it is still in the clinical trial process, and the overwhelming bulk of the drug that was available needed to go to the clinical trial, the company could not meet that demand.

We will also hear from people who have had some success in getting access to drugs that have not yet been approved, and we will hear different perspectives about what the impediments to access to drugs in clinical trials are.

Our job today, as Members of Congress, is to understand how the compassionate use system works and whether there is anything we can do to improve it. It is important to do this. Many patients are desperately ill, and they do not have the time to wait for a drug to make it through the clinical trials and approval process.

As we will hear today from our witnesses, access to drugs through compassionate use can save lives, but there are many limits on this system. One limit is the availability of the drug in the clinical trial stage. Often companies produce only limited amounts of an experimental drug. Sometimes that is because materials are in short supply, sometimes because a process is difficult, sometimes because they do not want to invest in a product with an uncertain future.

Then there are the limits of science. If a treatment is approved after phase II clinical trials, this would usually increase access to the treatment. In rare instances the data are so dramatic and the statistics so clear, that this is possible. For example, Gleevec, a treatment for certain types of leukemia, was recently approved after phase II trials. And ImClone is seeking approval of C225 for colorectal cancer after its phase II trials as well. But in most cases, it is necessary to conduct the larger-scale phase III trial to understand fully whether and how well a drug works and what the possible adverse effects are. It would be unethical to allow companies to market a drug as a treatment unless and until it has been appropriately tested for safety and efficacy. This is especially true in the case of life-saving treatments against such diseases as cancer and AIDS. So we are left with a very difficult situation, where



there are desperate patients trying so hard to get limited amounts of potentially life-saving drugs that are in clinical trials.

This hearing will raise important questions. How do we help patients get access to drugs that may help them? How do we assure that drugs are thoroughly tested for safety and efficacy, and how can companies be encouraged to consider treatment INDs at the early stages of the clinical trials so that patients can have access to a treatment as quickly as possible?

There are no easy answers here, but with the new and exciting developments in biotechnology, and important treatments on the horizon, these are the issues we have to address to make sure that as many people as possible are helped by these therapies.

I want to thank the witnesses for being here, particularly people on this first panel who are going to tell us about their own experiences. Mr. Chairman, I want to thank them all for being here, and I am looking forward to their testimony.

I do want to explain however, from a personal point of view, that there is a conflict that I have because of the California energy crisis. Our Governor's meeting with us at 1:30, so I am going to have to leave to attend that meeting, but I will get back here as quickly as I can.

We will have your testimony on the record. I will have a chance to review it. By having it on the record and your being here today, we can take what you have to say and go to our colleagues and tell them about any potential legislation or any other moves that we should be taking to solve the kind of situation that you have faced and try to make this problem one that will not be repeated over and over again.

So I want to apologize in advance for not being here for the whole hearing. I will try to get back as quickly as I can. But, Mr. Chairman, I want to thank you for this hearing. It is an important one, and I look forward to working with you on this very important issue.

Mr. BURTON. Thank you, Mr. Waxman. Mrs. Davis, did you have an opening statement you would like to make?

Mrs. JO ANN DAVIS OF VIRGINIA. No, thank you, Mr. Chairman.

Mr. BURTON. Mr. Kucinich.

Mr. KUCINICH. I wanted to thank the Chair for calling this hearing and welcome the witnesses. Certainly those of you who have a personal story to tell to this committee, who have experienced in a very profound and heartfelt way the impact of policies which have denied loved ones the opportunity to get help which was believed to be available, certainly have much to communicate to this Congress. I think that as Mr. Waxman said, your testimony will help guide the Congress in a direction which needs to be taken. In order to make sure that the access which has been denied people in the past can—the question of access can be resolved. So again, I want to thank the Chair for his sensitivity to these issues. I appreciate your ongoing commitment to public health. Thank you.

Mr. BURTON. Thank you, Mr. Kucinich. Mr. Cummings.

Mr. CUMMINGS. Thank you very much, Mr. Chairman, for your sensitivity to these issues. These are very, very important issues. And we as the Congress of this great country have a duty, I think, to address them.

The patients and their family members are frequently in search of information about the latest drugs being researched for effective treatment, and I represent the district in which Johns Hopkins is located, and, of course, we just had a major episode involving one of my constituents who died during the process of clinical trials. I guess that is how you would describe it. The people in the audience would know better than I do. But it shows the problems that we run into. We have to be very careful about the drugs and how they are used and when they are used. But on the other hand, we have situations where people are facing some very difficult circumstances in their lives, and I would imagine that at times people feel that perhaps the Federal Government goes too far in these trials.

To be very frank with you, I do not know that we will answer that question today, exactly where do you draw the line and where does a balance come? But the fact remains that there is a woman, a young woman in Baltimore, who was alive not very long ago, and now she is gone. She was healthy. And now she is gone.

And so I think this, Mr. Chairman, is an appropriate time for us to be looking at this issue. I am interested because I know that there are so many people who find themselves in the difficult circumstances that some of our witnesses do today, or their family members have.

And to our witnesses, I want to thank you for being a part of this hearing. In order for the Congress to do its work, we have to put a real face on our policy. So often we look at statistics and we hear numbers, but the real testimony comes when we are face-to-face with people who have been places where we have not gone. And so it makes it better for us to formulate policy when we hear from you. And so we take this moment as a Congress to thank you for being with us today, and I look forward to the testimony.

Mr. BURTON. Thank you, Mr. Cummings.

Mr. Santino, Mr. Burroughs, Mr. Baxter, Ms. Kellum, and Mr. Barr, we swear our witnesses, so would you stand and raise your right hands, please?

[Witnesses sworn.]

Mr. BURTON. Be seated. Mr. Santino, would you like to start? And I know that it is tough to say everything you want to say in 5 minutes, but if you could get as close to that as possible, we would appreciate it.

**STATEMENTS OF FRED SANTINO, ARLINGTON, MA; FRANK BURROUGHS, ARLINGTON, VA; DOUG BAXTER, WOODLAND, CA; SHANNON KELLUM, FT. MYERS, FL; AND DAVID BARR, NEW YORK, NY**

Mr. SANTINO. My name is Fred Santino. I am the husband of Ruth-Ann Santino, who just passed away May 5th. I have it boiled down to basically four points here: obtaining compassionate use, the information provided, the responsibility of drug manufacturers to communicate with patients, and manufacturers not being penalized for providing drugs to very sick people.

As far as the compassionate use, obtaining it, I do not feel there is any criteria by the government, by the hospitals, by anybody. I think there should be some criteria. When a new product is estab-

lished, part of the business plan ought to be what criteria am I going to have once we have success? In other words, they assume they are going to have success at some point when they make the drug. I assume that they are thinking that way, so let us have that as part of the business plan and let us demand it as a government, that we do that. I work for the government. We have policies. We have rules. We have to live by them.

Another point is how to find out about compassionate use. We found it is very difficult. It is not listed on any Web sites. It is not really clear where you would find out about it, how you would sign up for it. I happen to run four Web sites, and I had trouble finding the information. There are so many Web sites—I put it in my testimony, how many different Web sites there are. They are not linked. Some of them disagree. Some of them say trials are open. We were given a choice of four trials. None of them were listed. I do not know any of them as far as what manufacturers they were. I could not find anything about them, what side effects they were, anything like that. So I would like to see more information, and I would like to see the information managed somehow. Have one Web site tie them all together and have some sort of an update. If I am in the drug business and I am having a trial, I have got to update what is happening. Has there been serious side effects? Has there been successes? I would like to know, because a doctor offers me XQY322, I want to know what it is. I want to know who makes it, I want to know whether it is successful or not. I do not want it to be my decision.

The other thing is we were terribly ignored by a company, ImClone. I understand they were overwhelmed with responses, but in our case, three of my wife's letters were ignored. We wanted to know yes or no, can I have the drug? That is all. That is all we wanted was an answer, yes or no. I would have sent them the 34 cents to give me a postcard back. That is all I needed, but we were ignored. My sons wrote letters. I did not get a letter or anything back until we got a privilege number from the FDA and my wife was able to call the company, and she got a call back from a doctor saying that she would not qualify because she was too sick. Well, that took 3 months to get that answer, and we had other options. We could have gone to another drug at Sloane Kettering in the process, but we did not do that.

So I feel drug companies, if they are in the drug business, they have a responsibility to communicate with the patient. I happen to work for the Air Force. We put out an RFP for businesses, I do not know if 3,000 businesses are going to want that RFP, but we have to answer every one of them. So if I am in the drug business, I deal with patients, and those patients ought to be answered, and it ought to be mandatory. Otherwise, get out of the business.

My wife was sick. She said, "I'm a dying mother, and I want this drug. Can't you tell me yes or no?" How can you ignore a dying mother? How can you, Mr. Waksal? I don't understand how you can do it. My two sons wrote letters and you ignored them. How can you do that? Just say yes or no. I will give you 34 cents.

We needed the information to make decisions and we were not given it in time, so we missed out on other options, and I can see the drug business. I have a relative in the business, and I under-

stand their problems, but do not go in the business if you cannot communicate with people, and you cannot handle the business the way everybody else does. Go out of business. Let somebody else take you over.

I do not think you ought to be penalized for giving drugs to sick people. If my wife is real sick, give her the drug. Do not say my wife is too sick to have a drug. What is a drug for? I mean, really. We were told by ImClone that my wife had seven treatments and that would not qualify her. She was also told that by another clinical director at a hospital in Boston, that she could not get another drug, SU5416, she had too many treatments. But what are the drugs for if they are not for sick people, I mean, really?

That is pretty much all I have to say, and I think it can be improved by getting the information together, getting the people in a room like this. I thank Congressman Burton and the rest of the members of the committee for having this meeting, and I really think something ought to be done. And the reason I am here is I hope it will help other people, and nobody else has to suffer the way my family did. And I am really going to stay in this business for good until something does happen, so if anybody else needs my help, please call on me. I will be glad to help you.

Thank you.

[The prepared statement of Mr. Santino follows:]

**Testimony to Committee on Government Reform****June 20, 2001****(As updated July 3, 2001)****Fred Santino****Patients Obtaining a Drug Under Compassionate Use**

**Problem:** There are no procedures for patients to seek compassionate use of a drug. There is also no criteria for companies to judge who should be granted compassionate use. Companies can decide on their own who actually should receive their drug. The companies have no obligation to offer no explanation on giving the drug to one patient and not to another.

**Solution:** Drug companies must realize their social responsibility to provide a drug fairly to all or to none., or to establish specific criteria. If a drug has had some success, the manufacturer must realize that doctors are going to recommend the drug's use to patients who would potentially benefit. Compassionate use of a drug should be provided under some guidelines of fairness. For example, perhaps the sickest person or the one that has the most treatments already might have the highest priority. Perhaps a lottery is fair. If there is sufficient supply then all patients that need the drug, as determined by their physician, should get it.

**Drug Manufacturers Communications with Patients and Doctors**

**Problem:** If a drug has had some success, the manufacturer must realize that doctors are going to recommend the drug's use to patients who would potentially benefit. This may generate communications to the company, but the drug companies have not answered the letters in some cases. In other cases, companies have given out misinformation, such as telling patients that "a trial may be opening", and "there is no specific criteria to qualify". Companies don't have to respond to patients, they can simply ignore the patients' letters, letters from their doctors, and letters from their family members. In our case, three doctors called the company without success. It took a call from a congressman to the company to obtain all of the pertinent information.

**Solution:** Inquiries from patients must be answered so that patients can make decisions on treatment. If a drug is not going to be available, then the company must tell the patient or doctor so that they can make other plans. If a drug is going to be available, then the company should provide accurate information on qualification criteria, dates of availability, etc.

### **Companies Should Not be Penalized for Giving a Drug Under Compassionate Use**

**Problem:** Companies are reluctant to give very ill persons a drug under compassionate. My wife was denied further treatment based on the number of treatments she already had. A patient who has already had even one extra trial may not qualify for a specific trial. Trial directors are very specific about who gets the drug. Are companies worried about getting approval if they give their drug to very sick people? Why should companies seeking approval be penalized just for giving the drug to someone who is very ill and has no other options.

#### **Solution:**

Don't penalize companies that give out their drug to very ill people that have no other options. Allow companies to give out the drug to very sick people in addition to their ongoing clinical trials. The clinical trial itself can still be conducted in accordance with scientific/statistical purity, but it wouldn't consider those extra people who have been given the drug without meeting the exact guidelines. If one of the "very sick" people had a success, this would be a positive factor in gaining approval, but not a barrier to gaining approval if there was no success.

### **Finding Out About Clinical Trials and Compassionate Use**

**Problem:** There is so much information on trials that a patient or an advocate can't easily get the information they need. The government site is not always up to date. Trials listed "Open" are "Closed", and vice versa. Not all trials are listed. Compassionate use is not listed. Clinicaltrials.nih.gov is a good start, but there are so many more web sites by other organizations, manufacturers, and cancer centers that it is a tremendous burden to review all the sites. The sites often conflict with each other's information. There are so many sites that it is difficult to search them all. The information on them usually has some level of medical expertise. During my wife's cancer fight (over 2 ½ years) I spent a lot of my "spare" time searching the web for new drugs, trials, and general information on cancer. Even though I teach computer information systems and run 4 web sites, I found the information and search process to be overwhelming. What about patients and families that are less computer literate?

#### **This is a sampling of sites listing trials.**

<http://cancernet.nci.nih.gov/>

<http://cancertrials.nci.nih.gov/>

<http://www.fda.gov/oash/cancer/trials.html>

<http://www.cybermedtrials.com/>

[http://www.oncolink.upenn.edu/clinical\\_trials/](http://www.oncolink.upenn.edu/clinical_trials/)

<http://www.centerwatch.com/>

<http://www.jcrt.harvard.edu/>

<http://www.icare.org>

Manufacturers web sites

Cancer centers web sites

#### **Solution:**

Promote one web site as the "official" umbrella under which all others would be linked. Having a single starting point would help doctors and patients to find information. It would also help coordinate the information between sites. Require drug companies to keep up the information as a part of their business process. The sites should list more

information to help patients decide. Sites should provide information on results of clinical trials thus far, such as side effects, percentage of success, categories of success. If a web site is primarily for patients, then the terminology should be appropriate. Very few people have doctors or other medical personnel searching the web for them. It is primarily patients and their families that do the searching. Esoteric medical terminology should be avoided.

There should be one place to "sign up" for "compassionate use". Let patients register for possible "compassionate use", and if it becomes available later, let them know about it. If "compassionate use" is "open", then it should be publicly advertised on a web site so that patients can find it. If "compassionate use" is curtailed, then that should be advertised on the web site. In the case of Imclone, there was never any indication of "compassionate use" being open or closed on their web site.

#### **Public Responsibility and Sense of Urgency for Drug Companies**

**Problem:** In many cases companies have been granted exclusive rights to medical treatments through patents and/or fast track approval. These exclusive rights mean that they have authority over life and death for many patients. The actions the company takes can result in many people either living or dying. In the case of Imclone, Inc., they were granted a patent and fast track approval but have not been able to provide enough supply of their drug to satisfy the 10,000 requests they have received. Even worse, Imclone seems to have no sense of urgency, and has not made a reasonable attempt to increase the supply. Consequently, they are denying a lot of cancer patients the right to live, even though the technology to keep them alive exists. When Imclone received 10,000 responses from patients, didn't they feel a responsibility if they were unable to manufacture the drug themselves to seriously solicit contract manufacturing? With 10,000 inquiries from cancer patients, a public plea in the mass media would seem appropriate. In the case of Imclone, they were satisfied to wait for their new building to be built. I personally know of people involved in contract research and manufacturing for the drug industry. I have actually seen the unused capacity that Imclone could have used at one company. Experts tell me that there are other companies that would do contract manufacturing of biologicals. For a company like Imclone to provide their successful drug to just a few people here without any criteria or plan is highly irresponsible. The public is not being served by companies like Imclone that are just going to sit on thousands of inquiries from patients.

#### **Solution:**

Companies involved in drug development (such as Imclone) must realize that they have a public responsibility, even though they are a private company. Companies that have been given fast track approval or patents, and are unable to provide sufficient supply, should be encouraged to outsource to a contract manufacturing organization, team with an organization that has more resources, or even sell out to a larger company that can actually provide the drug to the 10,000 people who need it. Perhaps the FDA should consider a company's ability to manufacture in a reasonable time when evaluating

whether a company should receive FDA approval. When C-225 wasn't available "in a few weeks" as Imclone's "Hotline" was advertising, My wife missed other opportunities (such as Sloan Kettering's Immune Therapy Trial). After waiting so long for word on C-225, my wife had no choice to participate in other unproven Phase I trials that significantly deteriorated her condition, and probably hastened her death. According to my wife's doctors, C-225 might have saved her.



Mr. BURTON. I really, really appreciate you being here today. I knew about your story beforehand, and we will have some questions for you, but thank you very much.

Mr. Burroughs.

Mr. BURROUGHS. Good afternoon, Mr. Chairman and distinguished members of the committee and guests. I am Frank Burroughs, but for the past 21 years I have been better known as the father of Abigail Kathleen Burroughs.

Since February of this year Abigail ran out of options in her battle against cancer, which had spread to her neck and her lungs. I and others began to try and find treatment with experimental EGFR targeted cancer drugs.

We tried to get Abigail into narrowly defined clinical trials, but she did not qualify for them. We worked very hard to acquire the drugs on a compassionate-use basis, but got nowhere.

The drugs that we needed, the EGFR drugs that we needed were AstraZeneca's IRESSA and ImClone Systems C225, which statistically, and according to her oncologist, Dr. Maura L. Gillison at Johns Hopkins, showed a significant chance of helping her beat her cancer.

My only child, dear, sweet, loving, talented and compassionate Abigail died at 2:30 p.m. two Saturdays ago, June 9th. The loss of my beautiful compassionate child has left a hole in my life. Her mother, Kathleen, who took such good care of her, is of course, also very saddened, as is her dear stepfather, Gene Krueger.

There was hope, but no compassionate use of AstraZeneca's IRESSA or ImClone System's C225.

Abigail was compassionate. In her senior year in high school she won the distinguished Harry F. Byrd, Jr. Award for Leadership and Community Service for the Eight Virginia Congressional District. Abigail was an Echols honor student at the University of Virginia. Abigail cleaned toilets and changed beds in men's homeless shelters. Abigail worked in a poor neighborhood in Syracuse, NY, fixing up houses and running a free day camp for inner city children. Abigail started a major tutoring program for middle school children who were having learning problems. And this is the short list. Abigail was compassionate.

The world has lost a brilliant young woman who would have done great things.

I am here today because the issue of the wider use of compassionate use of drugs is a very important issue, because it touches tens of thousands of lives. Compassionate Abigail wants us to keep this issue alive, although we could not keep Abigail alive.

I know this is a money issue. I do not have all the answers, by the way, but I know it is a money issue, because some large pharmaceutical companies do have wider compassionate-use programs than others.

ImClone Systems has no compassionate use program. Multibillion dollar AstraZeneca has a very narrowly defined program, and it is very small. And Abigail, young Abigail, did not qualify for AstraZeneca's compassionate use program.

A very important role of industry and government is to help people and to save lives. We did not have a chance to get to save compassionate Abigail.

One idea I am working on I shared with Abigail on Thursday before she died. She fought till the end. She was a sweetheart. She was brave. She really liked the idea. Now, it is going to need some fine tuning. The idea is to set up a foundation or another vehicle to raise money from private sources, from the huge pharmaceutical industry, and from the U.S. Government, to provide money so that we can produce more of these new promising experimental drugs and have them available on a compassionate use basis.

From the knowledge I have, there needs to be a clear line drawn between clinical trials and compassionate use.

I am honored here to be with everybody on this panel, but Doug Baxter and I have become friends. Recently his 16-year-old son is fighting a battle with colorectal cancer. He has many difficulties getting into trials.

Abigail was compassionate. Abigail is now in the arms of God. Others, with the strength of Abigail's memory, beautiful memory, and I, will keep this issue alive so others may have a chance to live, a chance that Abigail, compassionate Abigail, did not have.

Thank you for inviting me here today, and thank you, dear Abigail, for giving me the strength to make it here today. Thank you.

[The prepared statement of Mr. Burroughs follows:]

**Testimony of Frank Burroughs  
for Hearing on Access to Experimental Drugs  
June 20, 2001**

**I am Frank Burroughs. I am better known as the father of 21 year-old Abigail Kathleen Burroughs.**

**Since February of this year, when Abigail ran out of conventional treatment options in her battle against squamous cell carcinoma that had invaded her neck and lungs, I and others began to try to get treatment for Abigail with promising experimental EGFR targeted cancer drugs.**

**We tried to get Abigail into narrowly defined clinical trials, but she did not qualify for them. We worked very hard to acquire the drugs on a compassionate basis and got nowhere.**

**The EGFR drugs we needed are Astra Zeneca's *Iressa* and Imclone Systems *C225*. Statistically and according to her oncologist at Johns Hopkins, Dr. Maura L. Gillison, these drugs had a significant chance of saving Abigail's life.**

**My only child, dear, sweet, loving, talented, and compassionate Abigail died at 2:30 PM two Saturdays ago, June 9<sup>th</sup>.**

**The loss of my beautiful compassionate daughter has left a tremendous hole in my life and has left me very sad.**

Her mother, Kathleen Dunn, who worked so hard and bravely, to care for Abigail, is also devastated. Her dear caring step dad, Gene Krueger, also shares our anguish.

There was hope, but no compassionate use of Astra Zeneca's *Iressa* or Imclone System's *C225* for Abigail.

Abigail was compassionate. During Abigail's senior year in high school, she was awarded the very prestigious Harry F. Byrd Award for Outstanding Leadership and Community Service for the 8<sup>th</sup> Virginia congressional district.

Abigail was an Echols honor student at the University of Virginia.

Abigail cleaned toilets and changed beds at a men's homeless shelter. Abigail worked on fixing up houses and helped run a free summer day camp in a poor neighborhood in Syracuse, New York.

Abigail started a major tutoring program for middle school children with learning problems. This is the short list.

Abigail was compassionate.

The world has lost a brilliant young woman who would have done great things.

I am here today, because the issue of wider compassionate use of hopeful experimental drugs needs to be given more attention.

**We did not get a chance to try to save Abigail's life. However, compassionate Abigail wants us to keep this issue alive, although we could not keep Abigail alive.**

**Part of my being here today is to learn more about this issue. In Abigail's absence, I and other people want to carry on this battle we started in February of this year.**

**I know that money is an issue. Some pharmaceutical companies provide wide compassionate use of their hopeful experimental cancer drugs.**

**Imclone Systems has no compassionate use program. Multi-billion dollar Astra Zeneca has a very small and very narrowly defined compassionate use program that young Abigail did not qualify for.**

**A very important role of the U.S. Government and Industry is to help people and to try to save lives.**

**We did not get a chance to try to save dear, sweet, talented, compassionate Abigail.**

**One idea I am working on I shared with Abigail on the Thursday before she died. Abigail really liked the idea.**

**That idea is to set up a foundation, or other vehicle, to raise money from private sources, from the giant pharmaceutical industry, and the U.S. Government to provide money to pay for more production of hopeful experimental cancer drugs to be distributed through compassionate use.**

From the knowledge I have, there needs to be a clear line drawn between clinical trial data that is vital for approval of new drugs, and compassionate use of experimental drugs.

However, data from compassionate use could be helpful in understanding a drug's effectiveness.

I am honored to be here today with Doug Baxter, young 16 year-old David Baxter's father. Another tragedy that 16 year- old David Baxter of Sacramento California is facing, his family is facing, and others are facing is that special David cannot get into Imclone System C225 clinical trials for his colorectal cancer, because he is under 18.

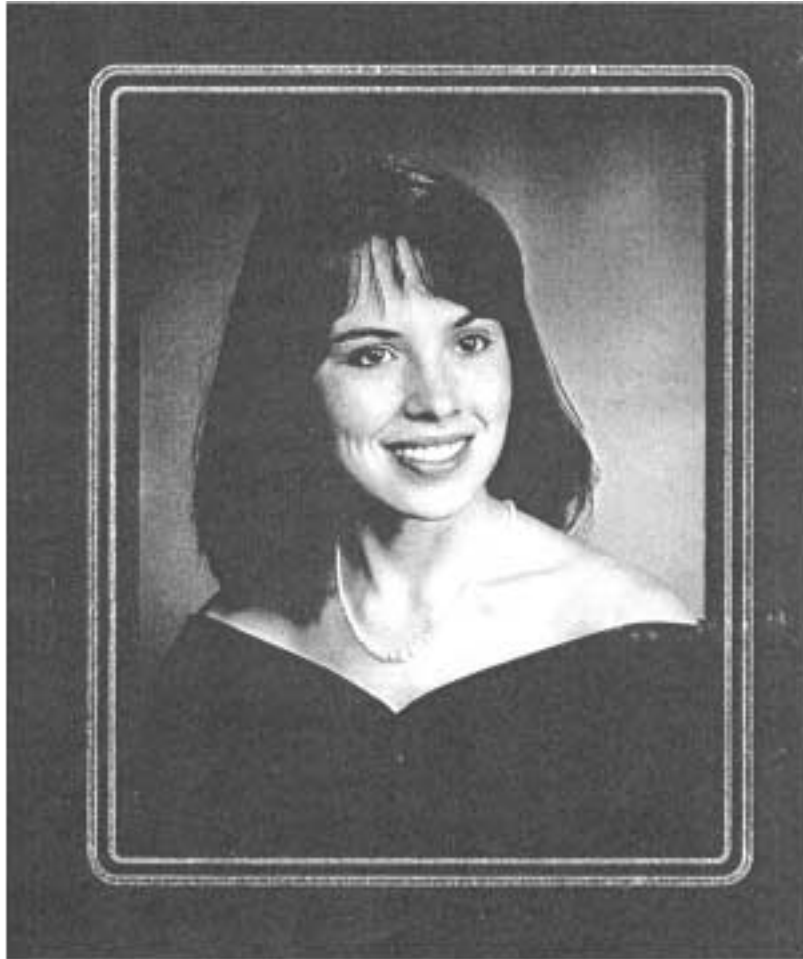
Also strict definitions of the trials have blocked David's access to a few trials that have waived the age requirement.

Abigail was compassionate. Abigail is now in the arms of God.

Others, with the strength of Abigail's sweet beautiful memory, and I will keep this issue alive so others may have a chance to live. Compassionate Abigail did not have that chance.

Thank you for inviting me here today.

Thank you Abigail for giving me the strength to make it here today.



TUESDAY, JUNE 12, 2001 **B7**

VIRGINIA

## Student Dies After Fight With Drug Firms

*Cancer Patient, 21, Sought Alternatives*

By STEVEN GINSBERG  
Washington Post Staff Writer

Abigail Burroughs, the University of Virginia student whose battle against cancer captured the spirit of an extended community stretching across the country, died of the disease in her sleep Saturday afternoon at her Falls Church home, family members said.

The 21-year-old honors student spent the final five months of her life struggling against cancer in her head, neck and lungs, and against pharmaceutical companies that refused to provide her with experimental drugs that some doctors said might have helped her.

Her story, and the efforts of those who fought to help her, quickly spread from her close friends to university students and faculty, local politicians, Capitol Hill, church groups and fellow cancer patients. People who knew her well and not at all became her life support.

Their contributions—big and small—were all equally meaningful, family members said yesterday. Virginia Sens. George Allen (R) and John W. Warner (R) sent letters to the drug firms on her behalf, and a group of Sunday school students in Southern Maryland mailed her personal cards and pictures. A petition that circulated through U-Va. was signed by more than 6,600 people. In recent days, sympathizers from as far away as Arizona sent words of support and offers of help to the family.

"There were lots and lots of wonderful people," her father, Frank Burroughs, said yesterday. "She very much wanted to get the word out that she wished she could thank them all."

Burroughs's final hours were spent in a recliner, where she rested for much of her last days. Her mother, Kathleen Dunn, said she talked about dying Friday night and awoke Saturday urgently requesting a videotape of "Tuesdays With Morrie," a television movie about dealing with death.

"I think she thought 'Tuesdays With Morrie' was something [that] would help" her parents, Dunn said. They did not get a chance to see it.

Burroughs's death was a bitter conclusion to her struggle for experimental drugs, friends and family members said yesterday. The companies she petitioned for months, AstraZeneca and ImClone Systems Inc., don't provide drugs for her type of cancer on a "compassionate use" basis—a program in which pharmaceutical companies provide unapproved drugs for those with no other options. After hearing about her case, OSI Pharmaceuticals, maker of an experimental drug that has shown promise for Burroughs's type of cancer, last week arranged for her to take part in a clinical trial—but it was too late.

Establishing a foundation to help others get drugs on a compassionate use basis was something Frank Burroughs and Abigail had talked about. Burroughs said he plans to launch it with the aid of people he has met in the last few months.

One of those people, Julian Grante, was on Capitol Hill yesterday lobbying lawmakers. "We're going to continue this fight in Abigail's honor to help other individuals and families going through this same thing," said Grante, senior partner in the Spotsylvania County law firm J. Irving & Draper.

Frank Burroughs said that he feels twinges of anger at the companies and their refusals but that he prefers to spend his time focusing on positives, as his daughter wished.

Yesterday he remembered trips to the zoo—Abigail so loved it that they went there eight times one year—and vacations to Disney World, Hawaii and Europe. The family also made many trips to Chincoteague, Va., where Abigail's parents, now divorced but united in their daughter's struggles, will take another ride sometime soon to spread her ashes, another of her wishes.

In addition to her parents, survivors include her stepfather, Gene Krueger, and stepbrothers, William and Christopher Krueger. There will be a viewing from 2 to 4 p.m. and 7 to 9 p.m. today at Murphy Funeral Homes in Falls Church.



Testimony of  
**Julian Irving Grante, Senior Partner**  
*J. Irving & Draper*  
 To the House Government Reform Committee  
 (Hearing on Access to Experimental Drugs)  
**107<sup>th</sup> Congress of the United States**  
**Washington, DC**  
**June 20, 2001**

Mr. Chairman, distinguished committee members, and guest:

Thank you for the opportunity to address the Committee today on important issues that directly impact millions of Americans of all ages, who are victims of various forms of cancer. As a cancer victim myself I can relate to the emotional pain and suffering an individual feels when they are informed that they have cancer. The process of treatment affects the cancer patient, their spouses, children, family members, co-workers, even the community at large. How lonely a place for a victim of cancer to be, with no family, friends or support system to lean on as they begin the steps of treatment and recovery.

My journey on the road to healing began on February 21, 2001, during a routine exam for prostate cancer. I asked my doctor for his advice on a swelling under my right arm that extended into my chest. My prostate exam was negative, but I was referred to a surgeon for an evaluation. The swelling under my arm was the size of a small grapefruit and was found to be a tumor. I had surgery at Mary Washington Hospital in Fredericksburg Virginia on February 26, 2001 and was diagnosed with Hodgkins Lymphoma, which attacks the Lymphatic system. This rare form of cancer often destroys the spleen, liver and lungs. On March 5, 2001 I went to George Washington University Hospital for a PET Scan, to determine if the cancer had spread to other parts of my body. I speak with authority when it comes to sharing about the pain and suffering of cancer, and the emotional impact it has had on me and my family.

Though there are days when I can hardly get out of bed in the morning, I still try to encourage others to have faith. Some days my joints begin to ache and feel weaker by day's ends. The results of my PET Scan came back positive, the cancer had spread to my spleen and on April 16, 2001 my spleen was removed. I am now on my 8<sup>th</sup> week of chemotherapy and my Oncologist Dr. Frederick Tucker is satisfied with my response to treatment. I thank GOD daily that I was fortunate to have adequate insurance to cover the high cost of medical treatment I've received so far.

I take several medications for pain daily and recently had to spend the night in the emergency room as my right hand was swollen like a baseball glove after my last chemo treatment. It was determined that I had a blood clot in my right arm. I take my chemo treatments through a port that was installed in my left chest just above the heart on May 9<sup>th</sup>. Today I feel well rested and have no apparent side effects from chemotherapy. I know that my faith in my Lord and Savior Jesus Christ will allow me to overcome the challenges ahead. I am blessed to be here to share with you today.

Several weeks ago I read an article in the Washington Post about a young woman named Abigail Burroughs, who was suffering from an extremely rare form of cancer called Squamous Cell Carcinoma, which attacks the head and neck areas. Abigail's cancer, was discovered in a tumor on her tongue last fall. Within three months after surgery, the tumor had recurred in the neck and she developed lung metastases.

After reading the article I contacted the reporter and called her father Frank, to see if I could be of assistance. We talked by phone for 2 weeks and finally met at his home in Arlington. My wife Jo and I after spending some time talking about Abigail, were given a tour of a proud father's library which was covered with Abigail's awards for academic achievement and civic responsibility.

I shared with my wife, had I not had cancer, I probably would have read the newspaper article and not given it another thought. Our daughter Jamil is 26, my son Dusan is 23, and Abigail's story could be their own. We also have a grandson Blake age 6, who through GOD'S grace and mercy I will live to see grow up and have a family of his own one-day.

Immediately after talking to Frank I began a campaign to assist the family in the acquisition of needed drugs that could possibly save Abigail's life. The campaign began with letters to **Mr. Carl-Gustaf Johanson, President AstraZeneca, USA, to supply IRESSA, Mr. Samuel Waks, President and CEO, Income Systems Incorporated, to supply C225 and Mr. Colin Goddard, Phd., President and CEO, O.S.I., to supply O.S.I. 774.** Over the past several weeks letters have been sent to President Bush, Vice President Cheney, Senior White House Advisor Karl Rove, Senators Warner, Allen, Hatch, Schumer, Clinton, Biden, Carper and Secretary Tommy Thompson@ Health/Human Services and Dr. Bertrum Spilker, Sr. Vice President of Scientific and Regulatory Affairs at PhARMA ( Pharmaceutical Research & Manufacturers Association of America) asking for their support.

I found it hard to understand that drug companies that had the medical resources available, to assist cancer victims, would offer little or no assistance to aid someone who was desperately hanging on to life, needing a miracle just to live a few months into a new year. Abigail was given just 9 months to live after her final diagnosis. The cancer had spread to her throat, lungs, and stomach. Radiation and chemotherapy had done little to end her pain. I thought that the hard line approach demonstrated by these companies to offer any hope to a 21 year old, who by all accounts had given so much to so many in her life time, was a sad commentary on corporate greed.

Where was the compassion, advertised in media campaigns to introduce new products? Compassion obviously has its limits. According to AstraZeneca, it refuses to make IRESSA available because it claims to lack data on the drug's effect against head and neck tumors like Abigail's. That a direct conflict of PhARMA'S position, that IRESSA is effective 54% of the time in treating head-neck cancers like Abigail's'.

Incline Systems justifies dropping out of the compassionate use program because "too many dying patients are beating at its doors for help" which distracts the firm from basic research.

What can be more important in research than giving hope to the dying, offering a glimmer of light to an individual who is suffering and with every second, every minute, every hour, every day gets closer to losing life's battle as their body is destroyed by the cancer within. I believe the time has come for the FDA, to make a monumental effort to work with pharmaceutical companies in the development of new guidelines on the availability of experimental drugs.

Partnerships between major pharmaceutical companies in the testing of new products could go a long way in helping smaller firms overcome the financial challenges of product research and development. At some point our society we must step up and place the highest value on human life. To make every effort to reduce, eliminate the pain and suffering of terminally ill.

Abigail wanted so much to live and devote her life to helping other people with cancer. Is it possible that the corporate executives at AstraZeneca, Imclone and O.S.I. have lost sight of why they invested their lives and financial resources in the dreams and goals of public service and pharmaceutical research? I pray not.

When my family and I last visited with Abigail and her parents on Memorial Day, she had a tremendous joy in her eyes, she was quick to laugh, to smile and give hope to others. I had arranged for Dale Solly from News Channel 7 to meet and visit with Abigail, to help through the media, to share her story. I remember her father saying over and over again, how happy and full of life she was that day. Abigail shared her short and long term goals, for recovery, which always included helping others. There were lots of pictures taken that day. Abigail was very warm and gentle as she talked to my grandson Blake and encouraged him to sit close for a picture. He told my wife and I that she was special.

On June 9<sup>th</sup> Abigail lost her race for a cure! Today is a good day to refocus our collective efforts, resources, time, energy and financial goals to reach out one to another in service to humanity, regardless of race, social or economic status. Maybe Congress could consider legislation to provide incentives to companies to develop compassionate programs, through grants and other national partnerships.

Today is a good day to remember Abigail and millions of other Americans who will benefit from compassionate use programs that can extend and improve the quality of life for victims of cancer and other life threatening diseases. On July 22, Abigail's family will have a memorial service to celebrate her life. I hope that we can also celebrate the victory of a new vision for the distribution of compassionate drugs!

Thank you,

Julian Irving Grante, Senior Partner  
***J. Irving & Draper***  
 10803 Heatherwood Drive  
 Spotsylvania, Virginia 22553  
 Phone: (540) 785-2279 or (540) 374-1600 Ext.357  
 E-mail, jgrante@cfsloans.com

## 'We've Gone From Hopeless to Hope'

*U-Va. Student Battling Rare Form of Cancer Gets Into Experimental Drug Program*

By STEVEN GINSBERG  
Washington Post Staff Writer

Abigail Burroughs, a University of Virginia student who has been fighting for months to gain access to experimental drugs to help her fight cancer, has been accepted to a clinical drug trial—if she has the strength to participate, her family and doctors say.

Burroughs's chance to take part in the trial in San Antonio depends on her physical ability to make the trip to Texas. And right now her prospects are not good, according to her physician, Maura Gillison of Johns Hopkins Hospital. Burroughs needs to be up and about at least half the time to meet the requirements of the trial, but she is bedridden 90 percent of the day, Gillison said.

Nonetheless, access to the trial ends a months-long struggle that has inspired friends, family members and thousands of people who have never met Burroughs to write letters and lobby the companies on her behalf. Among the efforts have been a petition signed by more than 6,600 people and a resolution passed by Falls Church City Council.

Gillison said she initially believed Burroughs's energy had been depleted by complications that arose while she was on a Caribbean cruise, a trip she was forced to abandon midway through, but "now I suspect more and more it's because of the underlying disease."

Burroughs has been in and out of the hospital since returning May 16, and she has not been able to eat.

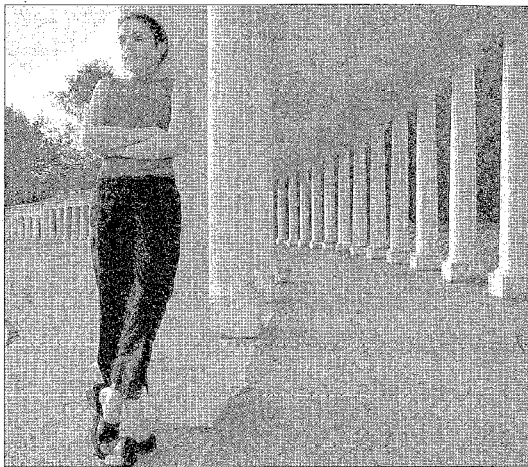
Her father said he is holding on to optimism.

"We certainly feel that we've gone from hopeless to hope," said Frank Burroughs, Abigail's father. "The other thing is we have this terrible fear that it's too little, too late."

Burroughs, a 21-year-old from Falls Church, is suffering from squamous cell carcinoma of the head and neck, a rare cancer for a non-smoker of her age. It first appeared as a spot on her tongue in fall 1999. After that was removed, it recurred in her neck last summer. Surgery, radiation and chemotherapy seemed to stop its growth, but this winter Burroughs learned the cancer had spread to her head, neck and lungs.

Doctors had no solutions this time, so the family sought experimental drugs.

Until now, however, Burroughs has been un-



Family members hope Abigail Burroughs, shown on campus, is strong enough to take part in the trial.

able to gain access to a clinical trial, and pharmaceutical companies had denied her pleas for compassionate-use programs, special provisions that make drugs available to those out of options.

At last, OSI Pharmaceuticals, a small firm in Uniondale, N.Y., and maker of the drug that doctors feel gives Burroughs the best chance, alerted her to the trial in San Antonio and helped her get into it, her doctor and family said. London-based AstraZeneca also has directed her to a new trial of its drug, Iressa, but it is unlikely Burroughs will take part in it.

"We are ecstatic and delighted for the family," said Kathy Gakante, spokeswoman for OSI.

New data on OSI's drug, Tarceva, released at

the end of May have shown encouraging signs for the type of cancer Burroughs has. Now Gillison fears her patient will be too sick to take advantage of it.

"Her greatest potential was five months ago," Gillison said. "If she was still the college student I met and had access to the drug when she was up and about, perhaps it could have prolonged her period of life." The average survival for her type of cancer is nine months, she said.

Burroughs's father said yesterday, "She wishes she could write everybody a letter and thank them for what they've done on her behalf."

He also assured her many supporters that "she's very much still fighting; she has not given up."



The Bunting Family ♦  
Family of Jacob and Hilda Blaustein Building  
Cancer Research  
1650 Orleans Street  
Baltimore, MD 21231-1000  
(410) 502-7142  
FAX (410) 514-9334

Maura L. Gillison, M.D., Ph.D.  
Assistant Professor of Oncology

March 8, 2001

To Whom It May Concern:

Ms. Abigail Burroughs is a 21 year old woman with a previous diagnosis of a Stage I T<sub>1</sub>N<sub>0</sub>M<sub>0</sub> squamous cell carcinoma of the anterior tongue. The tumor was treated with primary surgical resection. Unfortunately, she experienced a regional recurrence and was treated with a modified radical neck dissection followed by chemoradiation with high dose cisplatin. Within three months, the tumor recurred in the neck and she developed lung metastases.

She is receiving palliative Taxotere/CPT-11. Her tumor has been tested for EGFR expression by use of immunohistochemistry at LabCorp and showed >50% expression (3+).

We are searching for a clinical trial of an EGFR targeted agent for which she would be eligible or for a compassionate use program. Any help you may be able to offer would be greatly appreciated.

Sincerely,

A handwritten signature in black ink, appearing to read "M. Gillison", written over a horizontal line.

Maura L. Gillison, M.D., Ph.D.  
Assistant Professor of Oncology

MLG/amj



A Comprehensive Cancer  
Center Designated by the  
National Cancer Institute

Mr. BURTON. Thank you very much, Mr. Burroughs. And I really appreciate you being here, and I feel very sorry that you had to give this testimony.

Mr. Baxter.

Mr. BAXTER. Thank you. Honored Chairman, and committee members, I appreciate the opportunity to testify to you regarding our struggle with a pharmaceutical company to obtain a drug that my son needs.

It has been a difficult journey to get to this point, a difficult but short journey. In early March of this year, I took my son to Phoenix for our annual week-long trip to major league baseball training in Phoenix. We had a wonderful time. As usual, my son got a lot of autographs. It was a time of sunshine, joy, fun, normalcy.

The following week, David complained of some back pain, and the world was turned upside down when he was diagnosed with colorectal cancer. The doctors said they had never heard of this in a kid. It only got worse the next week when we found out that it had spread to his liver and lymph nodes.

He immediately started treatment and is now fighting the side effects of these treatments. He has had a positive attitude, but his smile has been few and far between lately as he struggles through this time.

David has doctors that have been great. We were excited as treatment began, only to cry as we saw the impact of these treatments. At times, David sleeps almost all day on the couch, only to get up when it is absolutely necessary, and to frequently take the morphine to make the pain bearable. Picture your child so sick and in such pain, wanting to help him, you just cry.

Cancer does not kill. It first embarks on a mission of relentless, relentless torture of hundreds of people, family members, friends, and strangers, compassionate strangers that step forward, wanting to help. His entire family suffers as David struggles. Because a child is hurting, his parents are consumed by the impacts of this process. We are consumed by trying to find help for David. Imagine the emotional extremes that we experienced, hearing David's doctor telling us of a promising drug that he was treating other patients with, that he even had that drug in his possession as part of a head and neck cancer trial. But he could not give it to David, because he could not give David the drug without the permission of ImClone Systems, Inc., a permission that ImClone has not yet allowed. ImClone has previously approved David's doctor to be a current investigator for this very same drug for neck cancer. ImClone has approved the facility where this doctor works, the Sutter Cancer Center in Sacramento. His doctor has provided a written request to the drug manufacturer requesting that he be approved as a co-investigator so he can participate in the colorectal cancer trial also, so my son could gain access to this.

There has been some discussions about perhaps having my son go East to participate in the colorectal cancer, where all of these clinical trials are being conducted on the East Coast only. But for a 16-year-old son, who has a prognosis of just a few months, it would be extremely cruel to take my son away from his family and friends to go back East and live in a hotel to do a colorectal trial.

For this reason, we would like to have permission for this cancer trial to be done also out West, where also people out our way could have access to this drug. We understand that there is a limited supply, and that this drug is important to move forward quickly. David's doctor believes that he could expedite the approvals through their investigational review board and not slow up the process. I hope that this can be looked into.

There are a number of possible things that we can consider. Compassionate use is a very important item, especially where there is available drug to be able to use that. But where the drug is in short supply, I think it is also important for the committee to look at ways of having this drug allowed in other geographical locations so that children such as mine can have the opportunity to participate in these clinical trials as well.

I thank you for the opportunity to speak with you this day, and I ask that the remainder of my testimony be entered into the record. Thank you.

[The prepared statement of Mr. Baxter follows:]

Douglas C. Baxter, P.E.  
871 W. Southwood Dr.  
Woodland, CA 95695  
(530) 792-5811 (w)  
(530) 668-9540 (h)

June 16, 2001

Committee on Government Reform  
2157 Rayburn House Office Building  
Washington, D.C. 20515-6143

Subject: "Compassionate Use INDs -- Is the Current Process Effective?  
Impact on a 16-year-old cancer patient -- David Baxter

Dear Honored Committee Members:

Chairperson and committee members, thank you for the opportunity to testify before you of our struggle with a pharmaceutical company to obtain a drug that my son needs.

How many Abigails and Davids will it take to bring about needed change? Abigail Burroughs, just 21 of Falls Church, VA may not have died on June 9, 2001 if she had been able to obtain the drugs her doctor wanted to give her but could not obtain. Abigail who lived a life of compassion for others did not receive compassion when she needed it most. Will my son, David Baxter, be the next Abigail?

YOUR CHILD: As I speak, please try to picture your young child or a child that you love very much having cancer. Picture your child having to go through the sickness of chemo treatments and suffering from burns within him from the radiation treatment. Picture your child at times only waking up due to pain and having to take morphine every three hours to cope with pain. My son has inoperable cancer in the rectum, which is unheard of in a child. It has spread to his liver and lymph nodes. His doctor says he only has a few months to live unless he starts responding to treatment. Cancer does not kill until it first does it insidious torture of the patient, family and loved ones.

THE STATUS: Congress needs to level the playing field so my child has a chance against the drug companies and their fleet of attorneys. A rule change is needed to improved access to drugs not yet approved by FDA. The pharmaceutical drug approval process needs to consider that there are children out there dying during the process. The FDA approval process lacks incentives and requirements of the drug companies to help those who will die during the waiting time for FDA approval.

ACTION NEEDED: Let's come up with a humane approach that is a win-win situation. All the available drug is used to help patients throughout the country and data is collected quickly to obtain FDA approval.

1. Compassionate Use. If there is an adequate supply of a drug being requested by a patient's doctor, the drug company should be required to provide the drug as



“Compassionate Use IND”. FDA approval would still be done. Priority should go to those who are not expected to live long enough for FDA approval, the youngest patients, and the patients with the best chance of long-term remission. The drug companies should be required provide the drug under “Compassionate Use IND” to the extent they can. If drug companies do not provide “Compassionate Use IND”, they should be required to document that they lack the financial or physical capacity as part of the FDA approval process.

2. Co-Investigator Use. Equally important is the need for a much broader availability of the drugs during the clinical trials. Should there be a limited supply of a drug available for clinical trials only (which would exclude compassionate use), then there should be a broader use of co-investigators. If the patient meets the requirements of the drug’s protocol and the patient’s doctor requests to be a co-investigator, the drug companies should be required allow this request to the extent necessary to provide reasonable geographical access to a clinical trial. Quality controls would be maintained at each co-investigator site. Children should not have to go thousands of miles for access to a drug they need.
3. Eliminate Age Restrictions Unless They Are Essential: David was denied access to an East Coast clinical trial because of his age. He is 16 and the protocol required that you be 18. Everyone just assumed that this was only an “adult cancer”. ImClone Systems, Inc. discussed the possibility of eliminating the age requirement but never did it because we indicated that it would be abusive to take David away from his family and friends, move across the entire country, and live in a hotel room for at least 4 months during the sickening chemo trial. This process would crush his positive attitude.
4. Require drug companies to use a standard process for listing all available clinical trials. Often doctors don’t have the time or don’t take the time to review what clinical trials are on going. Families and friends become very frustrated trying to do this research.

THE SHOCK – “YOUR SON HAS CANCER”. How did my journey lead me here today? In early March I took my son to Phoenix for our annual weeklong trip of watching major league baseball’s spring training. He had a wonderful time and as usual got a lot of autographs. It was a time of sunshine, fun, joy and normalcy. The following week David complained of some back pain and the world was turned upside down when he was then diagnosed with colorectal cancer. The doctors said they had never heard of this in a kid. It only got worst the following week when we found out that it had spread to other areas including his liver and it was an advanced Stage IV cancer. After a brief fight with the HMO he immediately started treatment and is now fighting the side affects of his treatment. He has endured a lot. He has a positive attitude, but his laughs and smiles have been missing for the last couple months.

THE FAMILY SUFFERS TOO: David’s doctors have been great. We had to do some fighting with the HMO to get David connected with the best oncologist for his age and type of cancer. We were excited and in great hope as treatment began only to cry as we saw the impact. At times David sleeps almost all day on the couch only to get up when it

is absolutely necessary and to frequently take the morphine to make the pain bearable. Picture your child so sick and in such pain and wanting to help him so much you just cry. Cancer does not just kill. It first embarks on a mission to relentlessly torture of hundreds of other people too. His entire family suffers as we see David in such a struggle. Because a child is hurting, his parents are consumed by impacts of the cancer continuously.

THE LOVE OF OTHERS: Our religion and the loving support of others have carried us. Love expressed by family, friends and total strangers provides an amazing strength when combined with our inner faith.

THE SEARCH FOR A SOLUTION: A parent with a child with cancer is consumed by an ongoing desire to help their child. Continuously searching for a solution and going through an endless roller coaster of hope and despair. A numbing search on the Internet. Innumerable phone calls to experts. Dozens of second opinions on every major decision. Loving friends calling with ideas – some good – some wild ones. You discuss these with your doctor and trust your doctor's final decision so you don't go insane.

THE AMAZING QUESTION: Why does a drug company refuse to approve a doctor's written request to be a co-investigator for a colorectal clinical trial (to give David reasonable access to the drug C255) when the same drug company has already approved the same doctor and cancer center to use C225 in a clinical trial for head and neck cancer??? The answer must be paperwork and money because the doctor is extremely well qualified, as is the facility, and FDA allows data of co-investigator sites to be included as part of the clinical trial. Approving this request would provide the same amount of data for the FDA approval process. The difference is possibly helping a child make it to see his high school graduation next year.

DAVID VERSUS GOLIATH: Imagine the emotional extremes of hearing David's doctor telling us he was involved with a drug that showed promise for treating colorectal cancer. That he even had the drug (just a few feet away) as part of a head and neck cancer trial, but he couldn't give us the drug without permission from ImClone Systems Inc. (ImClone), a permission that ImClone refuses to give. ImClone has previously approved David's doctor, Dr. Paul Rosenberg, to be a current investigator for the drug C225 for neck and head cancers. ImClone has also approved the facility where Dr. Rosenberg works, the Sutter Cancer Center, to be involved in the clinical trials. Dr. Rosenberg and other doctors have had encouraging results in these clinical trials. Dr. Rosenberg has written to ImClone (attached letter) requesting that he also be approved as a co-investigator for the colorectal cancer clinical trials that are currently only being conducted on the East Coast. David meets the protocol requirements to participate in the East Coast colorectal cancer clinical trials except for his age. ImClone indicated that they would change the protocol to eliminate the age restriction but said they would not approve another clinical trial location and he would have to go back east for four months, which would be extremely cruel to a child.

June 16, 2001

4

David's doctor has gone the extra mile trying to persuade ImClone to allow David access to C225. When everyone to date has gone the extra mile to help a child, it's unbelievable that a drug company can withhold access to a potentially life-saving drug. Dr. Rosenberg is confident that the Sutter facility's Investigational Review Board would approve his request to treat David as part of a clinical trial.

It is so ironic that if Abigail lived in our town, she could have received the drug C225 from Dr. Rosenberg's clinical trial in Sacramento that treats neck cancer and she would not have had to plead for the drug through compassionate use. Likewise, David would have access to colorectal clinical trials on the East Coast if he lived in Abigail's town 3000 miles away. Drug companies need to be required to have better geographical availability of drugs, at least for children during clinical trials by allowing more doctors to become co-investigators in these clinical trials. Because of the current policy, David's doctor can't give David a drug that he believes would be beneficial and that is already on his shelf.

Yes, congress needs to enter the arena and require reasonable access to these drugs through more co-investigator sites to provide reasonable geographical coverage and/or more compassionate use.

Thank you for allowing me to testify before you this day. It is not too late for ImClone and Congress to help David. I ask both of you to make a difference in my child's life.

Douglas Baxter  
David's Father

29, 1902 12:50pm -- From '4524503' -- Page 2  
 29/2001 TUE 13:21 FAX 4524503

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 LIN SOE, M.D.  
 TSUNG-NG W. TSAI, M.D.

May 23, 2001

Dr. Samuel Waksal, CEO  
 ImClone Systems, Inc.  
 180 Varick Street, 6th Floor  
 New York City, NY 10014

Dear Drs. Waksal and Needle:

As described in Mr. Doug Baxter's accompanying letter, we are caring for his son David Baxter.

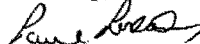
David unfortunately showed up at a remarkably young age (16) with an adenocarcinoma of his distal rectum which had invaded lymph nodes and liver at the time of its discovery.

David has failed infusional 5-FU and is currently being treated with CPT-11.

As you are aware, I am familiar with the use of C225 having used it for the treatment of head and neck cancers at the Sutter Cancer Center under an ImClone protocol.

I certainly would be willing to treat David with C225 here if you would be willing to agree to this. We would submit a protocol to our IRB for their approval if you would allow this. Thank you for your kind and prompt concern in this matter.

Sincerely,



Paul J. Rosenberg, M.D.

PJR:eg

cc: Dr. Michael Needle, Medical Director  
 ImClone System, Inc.  
 22 Chubb Way  
 Summerville, NJ 08876

Mr. BURTON. Thank you, Mr. Baxter, and I wish you well with David. Tell him that we understand, and that there is a lot of people up here thinking about him, and hopefully praying for him.

Ms. Kellum.

Ms. KELLUM. I am here today to share my testimony on how C225 has enabled me to be here today.

I was originally diagnosed in April 1998 at the age of 28. I was diagnosed with metastatic Stage IV colon cancer. It had started in the colon, but had already spread to other parts of the body. Throughout the next year, until April 1999, I received all standard therapies, as well as trials that were currently available that I was eligible for, none of which were able to even stabilize this disease at all.

In April 1999, there were no other options available. I was not eligible for surgery, and there was nothing out there that I qualified for. At that time my doctor introduced the idea of C225. At the same time he also mentioned that it had never been used in colon cancer before, and that I would be the first patient to receive it, but he would have to get approval from ImClone and go through the necessary process.

Fortunately, that answer was yes, and I started my first treatment of C225 in late April 1999. After four treatments, I received over a 50 percent reduction in the tumors, which nothing else had even phased. I continued to receive C225 over the next several months, having a total reduction of 80 percent. At that time my tumors became stable, and so I researched the possibility of surgery, which was necessary in the liver. That is where the disease was. I was eligible for liver surgery and had that in January 2000.

I am obviously very fortunate to be here today. It could very easily be my husband up here representing me and me not telling my story. If it was not for C225, I would not be here right now, and there would not be the opportunity for other people to have received it and for the knowledge that we have gained through this, and I am here representing all of you, and we need to get this drug approved, because no one should have to die.

Thank you for allowing me to share this testimony.

[The prepared statement of Ms. Kellum follows:]

**Testimony of Shannon Kellum****June 20, 2001****“Compassionate Use INDs – Is the Current Process Effective?”**

Diagnosed in April 1998 with Stage 4 metastatic colon cancer. I began chemotherapy at that time. By April 1999, I had tried all the standard therapies, as well as trials currently available, of which none were successful. I also saw a local liver surgeon to discuss that option. I was not a candidate for surgery either and realized there were no other options available. My oncologist, Dr. Rubin, mentioned C225 as a possible option. He had worked with C225 in the laboratory during the early 90's. He indicated it was not an approved drug and had not been administered to colon cancer patients, but he thought I may be a candidate anyway. The next step was to speak with Imclone and begin the approval process. After approval was sought, I began treatments and thus became the first patient (colon cancer) to receive C225. After receiving unsuccessful results from prior therapies, I tried to stay positive and hope for “good” results. This was my only hope. After receiving four treatments, I had a 50% reduction. Obviously overwhelming results. I continued to receive treatments over the next three months, at which time I had an overall reduction of 80%. At that time, the tumors appeared to stabilize. I then researched liver surgery again. I had liver surgery in January 2000.

I am very lucky to have received this drug compassionately. Because of this, it saved my life and gave hope to lots of other cancer patients. More importantly, the knowledge we have gained today and the steps that have been gained towards more innovative treatment are amazing. Therefore, my experience with a compassionate (single use) drug was quite extraordinary.

I realize how lucky I was to have received this drug, however, I understand that clinical trials are the “road” to getting INDs approved. Approval is the ultimate goal that we all should be focusing on because this is the only way to mass produce and distribute these drugs.

Mr. BURTON. Thank you, Ms. Kellum, and we are very happy that you are here as well, and you look like you are doing well.

Mr. Barr.

Mr. BARR. Thank you. My name is David Barr. I would like to thank you for the opportunity to speak with you today.

Mr. BURTON. Could you pull the mic just a little closer, please? Thank you.

Mr. BARR. I am a person with AIDS, and I am also an advocate for people with AIDS, and I have been working specifically on issues regarding treatment access since 1987. Access to experimental drugs is a particular concern to people with AIDS, because the disease is so deadly and its death so painful and humiliating. Most important, when AIDS first appeared as a new infectious disease in 1981, there were no standard treatments. All treatment was experimental, and early access programs were our only way of obtaining treatment. As research and drug development has progressed, there are now many treatments for HIV. However, these treatments are not a cure, they have limited effectiveness and can be too toxic for many patients to tolerate. And therefore, access to experimental treatments remains an important concern for people living with AIDS.

Beginning in 1989, the FDA began to work in earnest with patient advocates to develop standard for improved access to experimental drugs under compassionate use mechanisms and for accelerated approval of drugs to treat life-threatening illnesses.

Patient advocates are often included now as members or consultants on drug review panels, and directly involved at FDA's request in policy-setting discussions. Determining how to provide access to experimental treatments requires balancing several considerations. First there is the seriousness of the condition. In HIV we have patients who are on the verge of death and patients who will not feel ill at all for many years. These patients have different needs and need different solutions.

Second, one needs to consider what standard treatment is available and the usefulness of that treatment for the patient. If an approved therapy is available, there is no reason to risk taking a drug of unknown safety and efficacy.

And, finally, one must consider what is known about the safety, efficacy and dosing of the new drug. In weighing these considerations, one must take into account both the individual needs of a particular patient and the effect of access on a broader group of patients. An individual patient, faced with terminal illness, and often living in great fear and discomfort, may be more willing to risk taking an experimental treatment with little safety or efficacy data. However, making those decisions are never easy, and we usually make them with much less information than we would like to have.

Make no mistake. Although the FDA and drug companies may have an interest in the data from both studies in anecdotal use, no one needs this data more than patients. We are the ones who struggle with these life and death decisions. I would strongly urge that such data collection be continued, and in many cases strengthened.

Certainly, any member of the panel, when considering whether or not to take an experimental drug, would want to know if pre-

viously someone had toxic reactions and what success if any the drug had offered to other people.

I believe that industry claims that they are reluctant to participate in early access programs because of data submission requirements by the FDA are false ones. Such requirements are usually reasonable, not overly burdensome, and can provide useful information about the drug.

While the FDA can set standards for approval of early access programs and can later the proposed protocols under which experimental drugs can be made available, the agency has no authority to compel a company or sponsor to provide their drug to patients. Companies are often reluctant to do so. They are uncomfortable with any loss of control in the use of an experimental product. However, that is not FDA's fault. Prohibiting the FDA from collecting data in these situations would not likely increase a company's participation in early access programs. Companies are less concerned with data collection than they are with control over all the data and with drug supply. In fact, drug supply, particularly for drugs in phase II studies, is probably the most important and difficult obstacle. Patient advocates in HIV and other diseases have learned the immense value of working with companies as new drugs are developed. We have tracked the development of all HIV drugs from a concept to a test tube, through animal studies and into people, and we begin discussing the needs in terms of early access programs with companies as soon as phase I studies begin. And in this way, there is time to negotiate the real concerns about safety, dosing, patient entry criteria and drug supply, and it is only through those negotiations that such programs are a success. Rarely in my discussions with industry have concerns about the FDA and data collection been raised as barriers to early access development.

It would be unusual for a company to develop one policy around when or how to make experimental drugs available. Each drug needs to be considered independently based on the needs of patient population, what is known about safety and efficacy, dosing, and how the drug is manufactured.

I do not want to go over.

Mr. BURTON. Take your time. We just try to stay as close to 5 minutes as we can. We are not going to shoot you. [Laughter.]

Mr. BARR. Thanks. Thank you.

Patient advocates will often meet with company representatives while phase I studies are under way to discuss when and how an early access program can be created. The sooner those discussions begin, the better. When companies have refused to include early access mechanisms in their development plans, advocates have initiated letter-writing campaigns, demonstrations, and even boycotts to urge the company to reconsider. At least in HIV drug development most companies will bow to such pressure. However, the speed at which these programs are developed and the scope of who they reach, often leave much to be desired. Sometimes an early access program will not begin until an NDA is filed. And this means that the program will only run for a few months. Another situation is the entry criteria are so strict that many patients who need the drug are not eligible. Patient advocates to work with companies to



develop entry criteria that best meet patient needs. And very often the entry criteria will broaden as the program gets under way, and in this way, the company can determine if the demand for the drug will be greater than they are able to provide.

Again, the FDA has no authority to make these programs broader or begin earlier. The successes of single patient programs are more difficult to track because of the individual nature of the program. A treatment IND will include a protocol that will provide drug to all patients who meet the entry criteria, and physicians will enroll patients in the program and drug are distributed to the patients through the physicians.

Compassionate use single-patient programs are done on a case-by-case basis. There is no standard protocol, and that makes advocacy more difficult. Each individual doctor and patient must find a way for the company to provide the drug. Information about drug development in clinical studies is often available through patient advocacy organizations. And most important, is the new program from the National Library of Medicine, that has an online clinical trial directory, listing all public and private clinical trials in the United States.

The dire needs of one patient should not be used to set policy that can affect all patients. The difficult act of balancing the needs of an individual and the needs of many is fraught with problems. My impression is that the FDA, with scarce resources, frankly, does a good job at balancing those concerns. Most important, the idea that data collection is an obstacle to drug provision is false and harmful to patients. Data provides us with the only tools that we have in making extremely difficult life and death decisions.

Thank you.

[The prepared statement of Mr. Barr follows:]

**Testimony of David Barr, J.D., GWU Center for Health Research and Policy**

My name is David Barr. Thank you for the opportunity to speak with you today.

I am a person with AIDS. I am also an advocate for people with AIDS and have been working specifically on issues regarding treatment access since 1987. Access to experimental drugs is of particular concern to people with AIDS because the disease is so deadly and its death so painful and humiliating. Most important, when AIDS first appeared as a new infectious disease in 1981, there were no standard treatments. All treatment was experimental and early access programs were our only way of obtaining treatment. As research and drug development has progressed, there are now many treatments for HIV and the opportunistic infections that accompany HIV disease. However, these treatments are not a cure, they have limited effectiveness, and can be too toxic for many patients to tolerate. Therefore, access to experimental treatments remains an important concern for people living with AIDS. In fact, I currently take a drug available only through a Treatment IND program.

On October 11, 1988, I was one of the coordinators of a demonstration at the FDA. In fact, the demonstration was my idea. The AIDS Coalition to Unleash Power or ACT UP staged its first national action by seizing control of the FDA. The demonstration received international media attention and gave birth to an international movement of AIDS activism. We engaged in non-violent civil disobedience because we felt that, as people with a life threatening disease, the FDA was prohibiting our access to experimental treatment that might help us. While we did not know if such treatment was effective, we felt that we had to be given the option to take a risk with an experimental drug. Although there was danger in such a risk, we knew all too well the deadly certainty of the course of our disease, if left untreated. The demonstration was a success. Soon after, the FDA began to change its approval standards for Treatment IND. Further action led to the development of the accelerated approval regulations. Eight years after our initial demonstration at FDA, protease inhibitors – new, life-prolonging anti-HIV drugs – were approved faster than any drugs in the history of U.S. drug development.

Beginning in 1989, the FDA began to work in earnest with patient advocates to develop standards for improved access to experimental drugs under the compassionate use and Treatment IND mechanisms and for accelerated approval of drugs to treat life-threatening illnesses. Patient advocates are often included as members or consultants on drug review panels, and directly involved at FDA request in policy setting discussions. I have sat as a panelist several times on the Anti-Viral Drug Advisory Board.

Determining how to provide access to experimental treatments requires balancing several considerations. First, there is the seriousness of the condition. In HIV, we have patients who are on the verge of death and patients who will not feel ill at all for many years. These patients have different needs and need different solutions. Second, in order to decide when and how to make experimental drugs available, one needs to consider what standard treatment is available and the usefulness of that treatment for the patient. If an approved therapy is available, there is no reason to risk taking a drug of unknown safety and efficacy. Finally, one must consider what is known about the safety, efficacy and dosing of the new drug. In weighing these considerations, one must take into account both the individual needs of a particular patient and the effect of access on a broader group of patients.

An individual patient, faced with terminal illness and often living in great fear and discomfort may be more willing to risk taking an experimental drug with little safety or efficacy data. However, making those decisions are never easy and we usually make them with much less information than we would like. Make no mistake; although the FDA and drug companies may have an interest in the data from both studies and anecdotal use, no one needs this data more than patients. We are the ones who struggle with these life and death decisions. The more information we have at our disposal, the better. I very much see the FDA's request for reports on safety and, in some cases, efficacy in compassionate use and Treatment IND protocols as in the interests of patients. I would strongly urge that such data collection be continued and, in many cases, strengthened.

All patients, whether in an early or late stage of disease, must understand that their experience with an experimental product can provide important information for others about whether or not to take a risk. That information is essential for the FDA to meet its obligations to protect consumers from risks and dangers. Certainly, any member of the Panel, when considering whether or not to take an experimental drug, would want to know if previously, someone had toxic reactions, and what success, if any, the drug had offered to other people.

I believe industry claims that they are reluctant to participate in early access programs because of data submission requirements by the FDA are false ones. Such requirements are usually reasonable, not overly burdensome, and can often provide useful information about the drug. Drug companies, especially in the crucial mid-phases of drug development when questions about early access arise, are often afraid that any negative data will hurt their chances for drug approval or acceptance of a new product by physicians and consumers because of negative anecdotal reports. However, I do not think that such data is really harmful to an NDA unless it ought to be. When the FDA approved a Treatment IND for ddI, an anti-HIV drug, in 1990, 25,000 people with no other viable treatment options received the drug at no cost from Bristol Myers Squibb. It was through that program that we learned that ddI could cause life-threatening pancreatitis in some patients. This was not revealed from the controlled studies of the drug. This news did not interfere with the approval of ddI. It did, however, teach doctors how to use the drug safely. I take it now.

While the FDA can set standards for the approval of early access programs and can alter the proposed protocols under which experimental drugs can be made available, the agency has no authority to compel a company or sponsor to provide their drug to patients. Companies are often reluctant to do so. They are uncomfortable with any loss of control in the use of an experimental product. However, this is not the FDA's fault. Prohibiting the FDA from collecting data in these situations would not likely increase a company's participation in early access programs. Companies are less concerned with data collection than they are with control over all the data and with drug supply. In fact, drug

supply, particularly for drugs in Phase Two studies is probably the most important and difficult obstacle.

Patient advocates in HIV and other diseases have learned the immense value in working with companies as new drugs are developed. For years, we have tracked the development of all HIV drugs from a concept, to a test tube, through animal studies and into people. We begin discussing the needs and terms of early access programs with companies as soon as Phase One studies begin. In this way, there is time to negotiate the many real concerns about safety, dosing, patient entry criteria, and drug supply. It is only through these negotiations that such programs are a success. Rarely in my discussions with industry, have concerns about the FDA and data collection been raised as barriers to early access development.

It would be unusual for a company to develop one policy around when or how to make experimental drugs available. Each drug needs to be considered independently based on the needs of the patient population, what is known about safety, efficacy and dosing of the drug, and how the drug is manufactured. Patient advocates will often meet with company representatives while Phase I studies are underway to discuss when and how an early access program can be created. The sooner those discussions begin the better. When companies have refused to include early access mechanisms in their development plans, advocates have initiated letter writing campaigns, demonstrations and even boycotts to urge the company to re-consider. At least in HIV drug development, most companies will bow to such pressure.

However, the speed at which these programs are developed and the scope of who they reach often leaves much to be desired. Sometimes, an early access program will not begin until an NDA application is filed. This means that the program will run for only a few months. In other situations, the entry criteria are so strict, that many patients who need drug are not eligible. Patient advocates can work with companies to develop entry criteria that best meet patient needs. Very often, entry criteria will broaden as the program gets underway. In this way, the company can determine if the demand for the

drug will be more than they are able to provide. Again, the FDA has no authority to make these programs broader or begin earlier.

The successes of compassionate use programs are more difficult to track because of the individual nature of the program. A treatment IND program will include a protocol that will provide drug to all patients who meet the entry criteria. Physicians will enroll their patients in the program and the drugs are distributed to patients through the physicians. Compassionate use is done on a case-by-case basis. There is no standard protocol. This makes advocacy more difficult. Each individual doctor and patient must find a way for a company to provide the drug.

Information about drug development and clinical studies should be and is often available through patient advocacy organizations. The National Library of Medicine now has an on-line clinical trial directory listing all public and private clinical trials in the U.S.

The dire needs of one patient should not be used to set policy that can effect all patients. The difficult act of balancing the needs of an individual and the needs of many is fraught with problems. My impression is that the FDA, with limited resources, does a good job at balancing those concerns. Most important, the idea that data collection is an obstacle to drug provision is false and harmful to patients. Data provide us with the only tools we have in making extremely difficult, life and death decisions. I would urge the Committee not to take those tools away from us.

Mr. BURTON. Thank you, Mr. Barr. We will start out questions. We will proceed under the 5-minute rule so all Members have a chance. Let me start with you, Mr. Santino, Mr. Burroughs, and then the others, Mr. Baxter and Ms. Kellum can respond as well.

Did your wife and your son—your son and your daughter, start off with traditional chemotherapy treatment?

Mr. SANTINO. In my case, my wife started with standard treatment at a community hospital. And we thought everything was fine, and then 6 months later the cancer came back. She had to have another surgery. She had initial surgery, radiation and chemotherapy; 6 months she was free and clear, and then the cancer came back.

Mr. BURTON. But how long after she had her chemotherapy and radiation?

Mr. SANTINO. About 6 months it came back again.

Mr. BURTON. So was it in her lymph nodes; had it metastasized?

Mr. SANTINO. Not really. Initially it had not been, but then it went to her lymph nodes, and then when we ran out of options as far as standard treatment. We started looking around, other hospitals, other cities, other cancer centers, other whatever, to try to find something because at that point we were desperate.

Mr. BURTON. Then you started running into the wall.

Mr. SANTINO. Right, exactly.

Mr. BURTON. Mr. Burroughs.

Mr. BURROUGHS. Abigail had a rare type of cancer, that interestingly enough is starting to show up in young women at a greater rate almost monthly. It is still not a very common cancer. It started in her tongue, and it is the kind of cancer old men get who have been smoking and drinking their whole lives, very unusual in a young woman who was healthy.

We used surgery. They did not want to use chemotherapy or radiation because they thought there was no need to, it actually could cause more harm to her than not. Her cancer though came back last summer. She had surgery and major chemotherapy and radiation. It seemed to clear up for a while, and it came back in February of this year and got progressively worse. We ran out of other traditional drugs, chemotherapy drugs did not work for her. So we were down to the last wire, trying to get a EGFR targeted agent. The frustration was that these drugs, the kind of cancer she had and the cancer cells she had, and the high EGFR emissions that the cells gave off showed a real promise of reacting to these new drugs. It was very frustrating. It was like there was a lifeboat there, but we could not get to it.

Mr. BURTON. So when did you start trying to get the access to the—

Mr. BURROUGHS. We actually started trying to get the access in February, ahead of time, in case the chemotherapy she was on failed. And it did. And we continued our efforts. She was under another protocol, and that failed. And we continued trying to get these EGFR-targeted agents, which interestingly enough, showed greater promise for her than what was left on the conventional cancer shelf that was approved.

Mr. BURTON. But you ran into the wall, what, in February, March, where you could not get any positive response?

Mr. BURROUGHS. That is correct. We tried to get the drug, get her into trials. She did not qualify for the trials. The trials are very narrowly defined both for AstraZenica and ImClone. You know, prior treatments have an effect. For instance, AstraZenica's IRESSA, it is only for lung cancer that started in your lungs. Abigail's was in her lungs and her neck and elsewhere, but it did not start in her lungs, so she could not get into their compassionate use program, which, by the way, is very small. A lot of ImClone's trials, there are a lot of parameters, what kind of chemo had you had before, when had you had the chemotherapy, whether you could get into the trial.

Mr. BURTON. I understand. Mr. Baxter, is your son on traditional treatments, chemotherapy?

Mr. BAXTER. Yes, he is. David's cancer was quite advanced when they discovered it, because it is a cancer that you just do not look for in kids. And it had already metastasized by the time he was diagnosed, into his liver and lymph nodes. They started with radiation and 5-FU. That was not effective and showed continued growth during that time. And he has gone through some CPT-11 treatment. And what the CEA test levels are showing is that is still increasing as well.

Mr. BURTON. Have you tried to get some experimental drugs like through ImClone or AstraZenica?

Mr. BAXTER. Yes.

Mr. BURTON. And what kind of response have—

Mr. BAXTER. We and his doctor have requested C225.

Mr. BURTON. And what happened?

Mr. BAXTER. We got an e-mail message back. Also I received a phone call from the vice president of clinical affairs. It was courteous. He just simply explained that they believe that they could not do it.

Mr. BURTON. And, of course, you, Ms. Kellum, did get C225 after you had gone through traditional therapies?

Ms. KELLUM. Correct. I had already gone through all the standard therapies as well as any clinical trials that I was eligible for, and researched the option of surgery, which I was not eligible for at the time, and that is when I began C225.

Mr. BURTON. Well, I see my time has expired, and I will yield to my colleagues, but I want to find out today from you and from the ImClone company, and others, is why is this wall there, and whether or not the clinical trials—they may feel the clinical trials are jeopardized by giving it to people who would not qualify in the narrow definition of what the clinical trial is going to be. And if that is the case—and I would like to ask you this real quick if my colleagues let me ask one more question—did any of you get the feeling that they were worried about the clinical trial being jeopardized by giving you the drug, or did they give any explanation or do you have any idea about that? Because if that is the case, then what we want to try to do is figure out some way to protect the clinical trial while still giving the treatment to people for compassionate use.

Thank you, my colleagues, for letting me ask this question.

Mr. SANTINO. Congressman Burton, we got the feeling from one trial that we tried to get into, that my wife was too sick to get into



that trial. It was not C225. It was another trial of a drug called SU-5416. I got a referral from the FDA. They told me about it. And we did not have any idea whether it would be successful or not. It was just another drug that we could try, but the doctor point blank said, "No, your wife is too sick. She cannot get into this trial." But we felt behind the scenes it was the fact that the company did not want to risk their approval process possibly or mess up the statistics in the trial.

C225, we never got an answer on anything. Now, maybe they are protecting themselves by not responding, but we finally did talk to the doctor. When my wife talked in person to the vice president of clinical affairs, and he gave her a flat, "No, you could not do it."

"There is a clinical trial coming up at Dana Farber"—this was this spring—"but you do not qualify. You will not get in it." And her doctor had been trying to get that drug for 6 months for—three doctors had called ImClone trying to get it.

Mr. BURTON. OK. Mr. Burroughs.

Mr. BURROUGHS. Thank you, Chairman. Something that is interesting is that in a "60 Minutes" piece that was aired on May 6th, some—first of all, the two pharmaceutical companies, ImClone and AstraZenica, refused to be interviewed for that program. There was a quote—I assume it is correct—from AstraZenica, and that was that they were worried that compassionate use of their drug would interfere with the data from the trials. I am not an expert on FDA issues, but that was pretty accurate what their quote was on "60 Minutes", AstraZenica's.

If you think about it, you know, the data and the trial is data in the trial, it is empirical data, and that is what you use to get approval of the drug. Something outside of it is just extra data. They do not have to be tied together. Now, is that a problem? Maybe we will learn that from the FDA testimony. But on the surface, it looks like they should be two separate things. Thank you.

Mr. BURTON. Mr. Baxter, do you have any comment on that?

Mr. BAXTER. Well, I believe that in relationship to the C225, what I have been told is there is basically a shortage, and they would like to provide more of the drug to more people, but there is a shortage. They are building a large manufacturing facility. I certainly wish that could have started a few months earlier. Perhaps that needs to be looked at as to how we can increase production of these type of things earlier in the process, so that the Davids and others do not have to go through this process, because more of the drug would be available.

In my particular case, it goes beyond just compassionate use. It gets into compassionate co-investigators, allowing clinical trials not to be grouped in, you know, the Eastern part of the country, but allow access to other very experienced, very talented doctors such as David's doctor, who has already been approved by them. And we would like to know if—

Mr. BURTON. Out West.

Mr. BAXTER [continuing]. To know if there is a way that we can provide greater accessibility to these clinical trials through requiring more co-investigation locations.

Mr. BURTON. Did you have a comment, Ms. Kellum?

Ms. KELLUM. No, thank you.

Mr. BURTON. Mr. Horn, any questions?

Mr. HORN. Thank you, Mr. Chairman. I have appreciated the testimony that each of you have given. And I want to start with Mr. Santino.

You showed a picture of your family the day before Ruth-Ann passed. Your son told us that the hospice social worker arranged for the school principal to come to your home and give David his diploma so his mother could see him graduate. I know that must have been very important for Ruth-Ann. We hear a lot of reports that doctors do not make a referral to hospice soon enough. A report this week in the medical literature mentions that the doctors often times do not give accurate information about life expectancy when patients ask. What was your experience with this?

Mr. SANTINO. Well, right up to the end we had hoped that she would be somehow cured of all this. The last couple of weeks the doctor started talking hospice. He said, "You only have 2 weeks to live." And right away, you know, we went through the roof. You know, we had to tell the kids, "This is it. Mom is not going to be around any longer." And then the doctor changed his mind. He said, "Maybe you can qualify for another trial." And her condition got a little bit better. But we were still ready for the hospice. The hospice was there. Her condition did get—the doctor was wrong. The condition did get worse. His initial diagnosis was right.

The hospice arranged for the high school principal to come to her bedside in my house the day before she died, very important to her. She perked right up. My son felt that she was there at his graduation, and he got the diploma, and we had a little ceremony, and I think she was in peace after that. I think that was driving her to stay alive, to be at her son's graduation.

Mr. HORN. We also hear a great deal about cancer pain being poorly managed. What was your family's experience on the managing of the pain?

Mr. SANTINO. Well, the hospice helped manage the pain. They were experts in that part. When you go to hospice, you are saying, "I am not going to live any more. I just want to be comfortable." And they did a very good job at that. Everything was comfortable. Everything was counseling for the family, and I really cannot say enough for hospice. It was really much better than we would have had without them. I cannot say enough.

And we did not realize it was going to happen, but the hospice was there around us all the time, and every time I talked to them, I said, "Oh, no, I think you are wrong," but in the end they were right, and I am glad we had them, and managing the pain was definitely a good factor.

Mr. HORN. Mr. Santino, in the 1997 Food and Drug Modernization Act, Congress required the Department of Health and Human Services, through the NIH, to establish a registry of clinical trials for both federally and privately funded trials of experimental treatments for serious or life-threatening diseases or conditions. The Web site available at the [clinicaltrials.gov](http://clinicaltrials.gov), certainly lists about 5,200 clinical trials. Was this a resource you consulted? And if so, did you find it useful?

Mr. SANTINO. I claim to be an expert on Web sites, I guess self-proclaimed. But I run four Web sites myself. No, they are not help-

ful at all, because the information is not exactly accurate. If you go to the Web site, you will find that there are trials that are being offered—in our case, in Boston, Dana Farber, that are right there, that are being offered to you saying, “Do you want this trial?” You cannot find on any Web site anywhere. We were given four trials, basically alphabet soup to me, you know, just names. And I asked the doctor, “What do you know about these drugs?” “I do not know that much about them. They are just phase I trials.” They are not listed on the Web site anywhere. I could not find anything about it. And that is when really the Web site would be helpful to me.

On the other hand, my wife was given a drug called oxily platin on compassionate use. That was not listed on any Web site, so she was actually able to get compassionate use of that drug, but it was not listed anywhere. So there are things happening out there maybe too fast. I do not know. Maybe the Web site is a good idea, but it is not happening in a timely manner. Now, I think that is a Web problem, I do not think it is a drug problem. You find probably 50 Web sites, 49 out of them are out of date. So I do not blame the drug industry for that.

Mr. HORN. I believe we have a vote now, do we?

Mr. BURTON. Yes, we do. We have about 7½ minutes on the clock, so Members can go ahead and vote. And if you come back—I apologize to the panel. I hope you will bear with us. We will be back in about 10 minutes. We have to run to the floor for a vote, and we will be right back. And after we finish with you, we will go to the second panel.

We stand in recess.

[Recess.]

Mr. BURTON. We will call the committee to order, and would the witnesses please come back?

Is Mr. Burroughs out for now or did he leave? OK, well, we will wait just a moment on him then. Well, I will tell you, while we are waiting, why don't I go ahead and ask Mr. Santino a question.

Mr. Santino, did you and your wife look at complementary alternative therapies as well?

Mr. SANTINO. You mean like health food store, that type of thing?

Mr. BURTON. Well, yeah, and—

Mr. SANTINO. We talked to somebody at the Marino Center in Cambridge, MA, which is known for alternative treatments, but nothing really caught us. And the other thing is it interferes with chemotherapy. My wife was under chemotherapy all the time, so there were health food store type treatments available that are being used in Canada, but we never really—I think we bought one of them, but we never used it because—

Mr. BURTON. She was on conventional therapy.

Mr. SANTINO. Yes, and you have to be off chemotherapy for a while to use it, and we were not willing to experiment on our own. We were relying on the doctors primarily. If a doctor had told me to use it, I would have gone for it probably. But without the advice of a doctor, I would not do it.

Mr. BURTON. Was the chemotherapy—you said it was helpful at the beginning.

Mr. SANTINO. Yes. The very first treatment she had back in 1999. She had surgery April 1999 to remove the first tumor, and she had radiation and the standard 5-FU treatment, and that was very effective. She had no cancer for probably 6 months, and then November 1999, she had a tumor, another tumor growing, and she had to have a complete colostomy at that point, where she had only had what they call a resection of her colon. She still had use of her colon. But then she had a colostomy because of the surgery that came up just a few months after. She ended the treatment in August 1999, and the cancer reappeared in November 1999.

Mr. BURTON. But the doctors told her that the cancer was gone, and she—

Mr. SANTINO. Right, yes. We did not expect it to come back at all. It was worse than the first time because we thought we were out of the woods, and then, you know, summer of 1999, we were just, you know, soon as the chemotherapy and the radiation is over, we are back in business again as a family.

My wife actually went back to work in 1999. She was a teacher.

Mr. BURTON. I see.

Mr. SANTINO. She went to work for a couple of days, and then she was very sick. We are not even sure what she had at the time, and the tumor was probably starting, whatever was going on at the time. And she could not work again until fall of 1999.

Mr. BURTON. I see. Mr. Burroughs, did your daughter try any complementary or alternative therapies in addition to the traditional therapy she was using?

Mr. BURROUGHS. She was on a drug late in the game at Johns Hopkins called Herceptin, and I think that is a fairly new drug, if I am not mistaken. But we really were not able to get any of the new advanced experimental drugs.

Mr. BURTON. I was not just talking about the experimental drugs. I was talking about, you know, health remedies and things.

Mr. BURROUGHS. Going through this, is of course, a very difficult experience, and we just got flooded with nutritional information. "You should try oak bark juice." Sure. It has cyanide in it. Hello. You know, just everybody was trying to help, I guess, or maybe sell something or whatever, but there was just so much nutritional information, you start feeling like, am I overlooking something that could save her life? Then you realize there is no empirical data on it, and then you even look into some of it and find out that it is actually quite dangerous, or that it just plain does not work. But you feel like you have to sift through all this various piles of nutritional information that is coming to you from friends and wherever, because that could save her life, it could be some secret key here. Well, if it was so amazing, why have we not heard more about it?

Mr. BURTON. If you had one recommendation to make to the committee or the Food and Drug Administration or to the pharmaceutical companies, and I think that is probably one of the most important things we can ask you, what would you suggest? Because you have all been through it. What would you suggest?

Mr. BURROUGHS. That we do about the problem?

Mr. BURTON. Yes, as far as getting whatever is necessary to help your loved one or yourself in the treatment of cancer?

Mr. BURROUGHS. Well, you know, obviously, I have lost a treasure, my only child, and a beautiful child that she was—well, she is, but in a different world now. We need to have these experimental drugs available to more people now, or as soon as possible. If it is a money issue—I presented that in my testimony—that there are ways that we can put together some sort of vehicle or foundation or whatever to finance more production of these drugs. If it is a small company, they could even use the facilities of a larger company. There are ways I think to solve this problem.

Mr. BURTON. Production.

Mr. BURROUGHS. Yes.

Mr. BURTON. Mr. Santino, you have any?

Mr. SANTINO. I second what he is saying. I also think they have to be fair to people. You cannot be giving it out to one person and not giving it to another, especially at the same hospital. When my wife found out that somebody at Dana Farber at Boston was getting C225, and we were just anticipating it would not be available till November of that year, we went berserk, because here we are waiting for a drug for the fall. We got to keep my wife alive till the fall, and we find out somebody's already got it, right in the next chair to her. I mean, my God, how can a company be unfair like that? So, I mean, give it out to nobody, or give it out to all, and put the word out. Call the doctors at Dana Farber and say, "C225 not available." Then I don't have to write a letter. My wife wrote three letters, and none of them were answered. All a doctor had to do at the company was call Dana Farber and say that C225 is not available. We would have got the word from the doctor, because she went there every week.

I think the communications is lacking, I really do. I think they are not understanding that cancer patients are people. My wife was a wonderful person and she was a person. She was not just a name and an address and maybe a profit center. I mean, you are in the drug business, there are people there. So that is all I can say, is be fair to people and understand that there are people out there.

Mr. BURTON. Mr. Baxter, do you have any recommendations to the committee?

Mr. BAXTER. Well, I think that in the case of some of these pharmaceutical companies, that the request far, far exceeds the demand. And to take the position if you do not give it to everybody, do not give it—if you cannot help everybody, do not help anybody, is not being compassionate to anybody along the way. If they have an extra 200 pills, then put them to good use. I think that maybe the companies need to set a priority for compassionate use. We do not send children to war. I think we ought to take the extra step to make sure we protect children, that in establishing criteria, that children ought to have, for example, priority, those who have the best prognosis for a lengthy remission should have priority, and those who will, in all likelihood, die before the drug is approved should have the highest priority.

And then from that end you have to have some definition like that of who to help, but I do not think it would be right to say, OK, drug company, if you do not have enough drug to help everybody, do not help anybody, because that gives the drug company

a very easy way out of just denying compassionate use to everybody if that is done.

I think in large degree, it is a production issue. I believe that a company will not embark on a venture of hundreds of millions of dollars to build a facility to produce these drugs in a high-production mode until they know it is a slam dunk, that they have got it. And, you know, I think that perhaps we need to look at a—we have FDA approval, which we need to maintain that level of standard, but maybe there needs to be some kind of initial FDA approval, such as a probable approval level, in which a company, once they have reached that point, they can go ahead and start building their manufacturing facility with the blessing of the government as a backing. And should that drug not be approved, basically the cost incurred would be offset by a tax credit or something like that. We have to start production earlier in order to provide the most opportunity for the most people to participate in clinical trials and also to be able to receive compassionate use. We got to increase production earlier.

Mr. BURTON. Ms. Kellum, you have a—

Ms. KELLUM. Obviously, I am in a different situation than these gentlemen because I am here, and that is because I did receive C225. And I think what we all need to look at is this disease is what is unfair. I do not know if there is a fair or an unfair way of administering this drug, and I do not think ImClone liked saying no. But we need—I think we need to look at the common goal here and that is to find a cure for cancer, because if we do not have the cure, people are going to continue to die. And what is the answer to finding a cure. And I do not have that answer. I wish we all had a crystal ball that had the formula in it, but we do not. And I may be simplifying it, but I think we need to, you know, with a drug that has had this success, we need to get it approved as fast as possible and get it out to everyone. But denying some people the opportunity I do not think is the answer, because had I not gotten it, I would not be here today, and we would not have the knowledge or the capacity to give it to other individuals, so I think we need to take that into consideration as well. And, again, the common goal here is to find a cure, and whatever way we can do that, I think is in the best interest of all of us.

Thank you.

Mr. BURTON. Mr. Baxter, several years ago, a San Francisco police officer named Rick Schiff, his young daughter was diagnosed with a brain cancer. Her oncologist was aware of an experimental treatment that was showing some success in her type of cancer, but he opted not to inform the family of this treatment, instead pushing for another treatment option. Do you think doctors should provide families all of the options, standard, alternative, and experimental, and let the family decide?

Mr. BAXTER. I think that is very important. I feel I am very blessed with Dr. Rosenberg being my son's doctor. I believe that he has kept us in the loop. We have tossed some things off the Internet to him. He had explained why this would or would not be beneficial to my son, and we have been very blessed in having that type of relationship. And certainly, I would think personally it would be unethical for a doctor not to provide that information. It is ex-

tremely difficult though for a family to evaluate that, and so with that information needs to come the doctor's professional recommendations as well.

Mr. BURTON. Well, what we are talking about is making sure that everything that is open or possible to help—

Mr. BAXTER. Yes, indeed.

Mr. BURTON. Ms. Kellum, what do you say to those who haven't been able to access these experimental treatments or—I mean, you are very fortunate.

Ms. KELLUM. I am very, very fortunate, and I thank God for every additional day that I have, and it is very difficult for me to stand up here. And in some ways I do feel guilty because I am still here, but I am human, and that guilt is there. But I also feel that this is a chance for me to help get these drugs approved quicker and to share my testimony, and to just do whatever possible to find a cure. And again I go back to that. We do not have a cure, and I think that is why we are all here, is to find one.

Mr. BARR. Excuse me. Could I address the fairness issue that you asked?

Mr. BURTON. Sure.

Mr. BARR. I think that there are two issues. One is that the FDA really needs to discuss with sponsors the need for an expanded access program at the earliest possible stage, at the submission of an IND.

Mr. BURTON. And they did that with the AIDS epidemic.

Mr. BARR. And I think making sure that those discussions happen—and a company might do it, a company might not do it, but urging from the agency is really important. And the treatment IND mechanism is probably the best way for insuring fairness in decisionmaking across the board, because there what the treatment IND mechanism does is it provides both the agency and the sponsor and the patients with an infrastructure for how decisions are made because a protocol gets created and you want the protocol to not interfere with clinical trial enrollment, and you want it to reach those patients who have no other treatment options and who need this most of all. So using that mechanism is probably the best way for providing a framework for decisionmaking that then is not arbitrary and helps some patients and not others.

Mr. BURTON. Well, let me followup what you just said with a couple of questions. The AIDS community has shown the world that when life is at stake, sometimes rules do not matter quite as much. There were peaceful protests, sit-ins, coming together as a community to demand access to care. So what do you say to those who would say that providing access to experimental drugs outside clinical trials may be dangerous?

Mr. BARR. Well, I was the coordinator of a demonstration at the FDA in 1988, and the demonstration was, I guess, my idea, where we actually seized control of the FDA because we felt that they were not doing what they needed to do to provide us with the ability to make decisions about whether or not to take risks. What we were able to show—and through the work that—through the advocacy work that was done, the agency really began to move and change its position. And at least if you look at the expanded access programs, early access programs that have been used in HIV, we

have been able to show that those programs do not interfere with clinical trial enrollment, and they do not interfere with the running of the clinical trials. Any efficacy data that would come out of an expanded access program would really have no effect on a clinical study. Safety issues might have an effect on a clinical study, if, for example, you had an adverse event come out of a drug that was being given on a compassionate use that was not seen in a clinical trial. That might affect what happens in the clinical trials, but then again you might want it to because the adverse event could be very, very serious, and you would certainly want to at least incorporate looking for that toxicity in the clinical study. But those programs have not affected clinical studies in HIV in a negative way.

Mr. BURTON. Bastyr University, which trains naturopathic doctors was the first naturopathic college to receive NIH funding. Their research center was funded to look at alternative medicine use in the HIV/AIDS community. Do you integrate complementary and alternative therapies into experimental treatment?

Do you integrate complementary and alternative therapies into your treatment protocol, and what advice would you or do you share with others about different approaches to health maintenance while living with AIDS? And I think all of this is relevant to the cancer question.

Mr. BARR. The issue of alternative therapies is I think very complex because there is growing interest among patients in using alternative therapies, unusually as complementary drugs or therapies to what their doctor is prescribing. Very often the doctor will not have very much information about alternative therapies, sometimes just because it is not an area of expertise for the doctor, but most often because we do not have very much data on the use, on the effectiveness and safety of alternative therapies, which can be just as toxic as any pill produced by Merck or Bristol Myers Squibb, and AIDS advocates have strongly urged that alternative therapies be subject to the same kinds of rigorous controlled clinical studies to determine what their safety and efficacy is as any other kind of drug.

I think what is most important is for doctors to always ask their patients about whether or not they are using a complementary therapy or an alternative therapy, and then look into the possibility of dangerous drug interactions and what possible side effects might arise from the alternative therapy. Very often patients feel that those kinds of therapies are beneficial to, if not the disease that they have, in alleviating some of the side effects from the drugs that they are taking for their cancer or for their AIDS. And I think also that those kinds of treatments are very important in helping patients feel more empowered in taking more control over their medical situation, but it is really important that they discuss them with their doctors and that doctors ask about that stuff.

Mr. BURTON. Mr. Burroughs, for our record here, did AstraZenica and ImClone Systems communicate clearly with you?

Mr. BURROUGHS. That was a big problem we had. No, they did not. We got an awful lot of run-around, "Oh, call this 1-800 number. No, call that 1-800 number. I'm sorry. This person is on vaca-



tion.” “Well, is there someone that can cover for them?” “No, they will be back in a week.”

There was really poor communications. It was ridiculous. That is the short version of the story, that it took so long to get feedback on a question.

For instance, with AstraZenica, maybe I mentioned it earlier, that Abigail’s story, her situation, was actually brought up at a board of directors meeting in London, and I never heard any feedback from it, what was decided. You know, what did they say? Why couldn’t you tell me that, tell me something? Communications was very slow. It was confused. And I was never able to get something printed like, “Here is our policy on compassionate use,” or “Here is our definition of our compassionate use policy,” and “These are a list of trials of our drugs,” either from ImClone or from AstraZenica.

Mr. BURTON. So they really were almost nonresponsive?

Mr. BURROUGHS. Well, it took a long time to get answers to a question like, “What is AstraZenica’s trial about?” And it took, you know, a week and a half to find out that it is only a few people in it, it is just for people who have lung cancer and only lung cancer, but it took me a week and a half to find that out. I found out from ImClone, someone at ImClone, after going through a number of different people, that there was a clinical trial in Fairfax, VA. And I find out that, oh, great, so I have this great hope. But that is all the information I had. “Well, here is the number to call in Fairfax.” And I call the Oncology Center of Fairfax, and find out that Abigail does not meet the parameters of the trials. Why can’t this information be clearly communicated on a few pieces of paper or whatever to me, or an e-mail or whatever?

Mr. BURTON. So I guess the next question is irrelevant. ImClone and AstraZenica did not provide clear enough dated information to you on the company sponsored trials?

Mr. BURROUGHS. That is correct.

Mr. BURTON. And they did not give you any information on the requirements that she would need to get into the trials?

Mr. BURROUGHS. We had to find those out for ourselves.

Mr. BURTON. OK. Anything else? Mrs. Morella. OK, Mrs. Morella, go ahead.

Mrs. MORELLA. Thank you, Mr. Chairman. Thank you for arranging this hearing. I want to thank all of you who have testified on this first panel, for sharing your stories with us. Indeed, you bring a real human dimension to the issue, and that helps focus attention on it through the stories that you have told.

Mr. Santino and Mr. Burroughs, I offer my sympathy to you on the loss of your daughter and your wife. And reading about and hearing about your son, Mr. Baxter. And the fact that you are doing well, because of C225. And, Mr. Barr, I hope that you will continue to do well. It is an area I have been very much involved with, that area of HIV and AIDS, and what we can do.

Mr. Santino, I grew up in Somerville, MA. Matter of fact, I know St. Clement School. I read the article that your son wrote about it, so I can identify very much with—

Mr. SANTINO. What a coincidence.

Mrs. MORELLA. I am sorry?

Mr. SANTINO. What a coincidence.

Mrs. MORELLA. It is indeed. That brings us even closer together. I also have the National Institutes of Health in my district and FDA, Food and Drug Administration.

And I was listening to your response to the questions that the chairman has asked, and they are pretty much some of the concerns I had, trying to figure out before we go to our administrators, FDA and ImClone on the next panel, but what you see needs to be done. And I guess I can deduct from what you have said—and you can tell me whether I am right or whether something should be added—but first of all, there is, I think as you have said, Mr. Barr, no standard protocol for compassionate use of new drugs. If you are not in a clinical trial, then it is helter skelter whether your doctor knows about it, whether you find a Web site that happens to be accurate at that moment, whether there is someone else who links you up with a possibility of being looked at on a case-by-case basis for being eligible, whether there is an adequate supply that is available.

And so it seems to me that maybe one of the questions we will want to ask the second panel is, “Are you working on establishing some process that people would know about and making sure that there is information available?”

I also discern that not all doctors know about the various clinical trials in those areas, so it seems as though maybe the professional reaccreditation or what doctors do to get the professional training, should make sure they are including how to be up to date in those particular areas.

So I want to give you an opportunity to comment. Is there anything I am missing in that dimension when I look to what we would ask the next panel to help to clarify this situation, Mr. Burroughs?

Mr. BURROUGHS. Thank you. Something I tried to bring out in my testimony was that I do think that part of this issue is money. Isn't that something that affects so many things? I think that, for instance, what I also brought out in my testimony is that some companies do wider compassionate use of drugs than others. Some do not do any. It is an issue of money. The companies do not want to spend the money to make more of this drug, because they are not going to make any money off of it. But there is a way to solve that problem. And not to make anybody the bad guy here, why do we not all work together? Why do we not have the pharmaceutical industry, the government, other private sources or whatever, solve the money problem, because it is expensive to make these drugs. I do not have the exact answer, but I brought that out in my testimony that some sort of foundation or other vehicle to provide the funding to make more of these experimental drugs.

In the case of Abigail, statistically, there was a 54 percent that AstraZenica's IRESSA could have saved her life, and we could not get the drug. On the other hand, there are companies like Pfizer and Bristol Myers Squibb and Burroughs-Wellcome, do quite a bit of compassionate use of drugs. I think it is a money issue.

Mrs. MORELLA. Maybe it would be appropriate to have a conference or some kind of a meeting where you get these partner-

ships, the Federal Government for its role, the private sector, individuals, who could come together and——

Mr. BURROUGHS. Pharmaceutical industry. Yes, I think that we do not want to make anybody here the enemy. That never does anybody any good, but we want to take the resources we have in the pharmaceutical industry and government and elsewhere, and come up with a funding to help make more of these drugs. If there are FDA rules that affect the application or the availability of compassionate use, let us solve that problem. I think it is a solvable problem. Thank you.

Mrs. MORELLA. Would anyone else like to comment? Mr. Santino.

Mr. SANTINO. Mrs. Morella, I question the process. Why does somebody like myself or Mr. Burroughs have to go off on their own and do the research, when it should be a medical person? I do not even know what I am talking about when I look at a medical Web site, like make a call to a company. I did not know what carcinoma was, for example. How would I know what that is? Because I am an engineer. Why should I—I mean, if I have an aspirin, I ask the doctor, and he says, “Take the aspirin, OK?” I do not have to call the company and say, “Is it all right for me to take the aspirin?” You know, I deal through an intermediary who is a medical person. I mean this is such an awful disease we are talking about, in my case, my wife’s colon cancer. Why should I be on the phone calling companies or writing letters or, you know, making ImClone the bad guy, when maybe the medical community should have solved that way before. So when ImClone is offering the drug under compassionate use, let them tell Dana Farber Cancer Center or whatever cancer center, about that, and take me out of the loop. I mean, now, I do not have a wife. I do not have an advocate. If I get cancer, I have to do it myself while I am sick. I did it for my wife because I was well and she was sick. I could do it. I could do all the research and the digging and whatnot, but I question why does the family have to do that in the first place? Is this the same for every disease? I mean, I do not even know.

Mrs. MORELLA. Dissemination of the correct information to the parties involved has definitely got to be one of the major points that will come from your testimony.

I just want to—I’m sorry. Mr. Baxter.

Mr. BAXTER. I believe that FDA is endeavoring to do a very good job within the framework that they now exist, and the approval process is obviously important for society at large, but I think that also it is important to look at the risk factors versus approval. As a drug goes toward approval, progressively they know more and more about it. Progressively they know the risk and stuff like that. And so you get up to a point where, OK, this is FDA approved. But at the same time, it is like my son having a scratch on his arm, and the other arm being chopped off and bleeding to death. I mean, while we want to make sure you are not going to get any infection in this scratch while he is bleeding.

I think it is important also to realize that progressively my son’s prognosis is becoming progressively more skeptical, and so the risk of him dying becomes greater and greater all the time. So at some point, especially—I do not know if there is another step or another classification of approval, say, for terminally ill patients that FDA

approval could be authorized for those patients that have been classified, and which by far the risk of death from the actual cancer far exceeds any potential side effects and stuff like that. But I think that for the terminally ill, that type of hope, because if a patient does not have hope, they are lost, you know? They need to have a level of approval perhaps that is a little bit different for those who are terminally ill, and maybe that is something that needs to be looked at as well.

Mrs. MORELLA. That is a very good point, and I think it is one that should be posed to the second panel. Thank you, Mr. Chairman.

Mr. BURTON. Mrs. Davis.

Mrs. JO ANN DAVIS OF VIRGINIA. Thank you, Mr. Chairman, and thank you all for coming and testifying today. I know it has to be difficult for some of you. And, Ms. Kellum, I would just encourage you to not feel guilty because you were able to be helped, because I think it is good that you have the testimony that the drug did help, so that now it can hopefully help others.

And Mrs. Morella touched a little bit on what I wanted to ask, was until—actually, until I read the article about your daughter, Mr. Burroughs, I was not familiar with compassionate use drugs. And I guess my curiosity, my question is, how did you—how did any of you know about compassionate use drugs? I mean, how did you know who to contact? How did you know who had them and whatever, because if I remember correctly, in the article, the first two, ImClone and—

Mr. BURROUGHS. AstraZenica.

Mrs. JO ANN DAVIS OF VIRGINIA [continuing]. You could not get, but then I think the week before she passed away, another pharmaceutical company heard about her case and came up with a drug, but it was too late.

Mr. BURROUGHS. About 2 weeks before Abigail died, she got into a trial of OSI Pharmaceuticals, OSI-774 in San Antonio, TX. They are a very, very small company, but I will tell you, they really kept in touch with us, and as soon as they had the drug manufactured, as soon as they had a trial open, they called us. Now, I know they are small, but I think a big company can have good communications too. These people were absolutely wonderful. The problem we had was it was too little too late. Abigail was not strong enough to make it to San Antonio to be—she could not even do the traveling let alone be in the trial. She died 2 weeks after we got that news. But that was OSI Pharmaceutical, very small, little company.

Mrs. JO ANN DAVIS OF VIRGINIA. And I guess that brings to the question of how did you know? How would you have known to have contacted OSI? I mean, how did any of you know to contact—

Mr. BURROUGHS. What is interesting, what you do is you learn a lot from working and talking to people. You keep gaining more and more knowledge. Initially we knew about ImClone's C225 and AstraZenica's IRESSA from her oncologist, Dr. Maura L. Gillison at Johns Hopkins. And she says, "It is going to be hard getting these if you can get them at all. You better get working ahead of time before Abigail is off of the current chemotherapy as a backup in case it does not work."

We got to work right away, believe me. And we started learning how difficult it was to get into narrowly defined trials, how compassionate use is almost nonexistent in both companies—well, it is nonexistent in ImClone. It is almost nonexistent in AstraZenica. OSI Pharmaceutical is a very tiny little company. They were, like I said, wonderful, but the way we found out about them was I made a phone call from a suggestion from a friend of mine to call the Dana Farber Cancer Center up in Boston at Harvard University, and I got hold of some nice people there that said, “Have you heard of OSI Pharmaceutical?” I said, “I have done a lot of Web site searches on EGFR-targeted agents, believe me, and I have had people—and they just did not show up on the radar screen.” And they were a late player in the game, but they came through for us once they had the drug manufactured and helped us—kept in touch with us. They were wonderful people, very good communications.

Mrs. JO ANN DAVIS OF VIRGINIA. Mr. Chairman, I guess that is my point I wanted to have made, was that when I was speaking to a young lady in my office who had cancer, and she, by the luck of the draw, someone she knew had heard that she had cancer, and she happened to have been on a Web site and saw a drug, and then told her about it, and then she was able to go and get into an experimental program and had success like Ms. Kellum did. Not the same type of cancer, but that is the point, and I think Mrs. Morella touched on it, is that as, you know, the people who have cancer in their families, why are they having to search the Web site to find out if there is anything that can help them?

And, Mr. Baxter, I will tell you, I have a 19-year-old son, and I cannot imagine what you are going through, and my prayers will certainly be with you.

Mr. BAXTER. Thank you.

Mr. BURTON. Thank you very much. I appreciate your patience.

Mrs. JO ANN DAVIS OF VIRGINIA. I think we have another comment, Mr. Chairman.

Mr. BURTON. Oh, I am sorry.

Mrs. JO ANN DAVIS OF VIRGINIA. Not me. Mr. Santino.

Mr. SANTINO. On the compassionate use, we had both the good and the bad. And the way it should work is the way it worked for us the first time. My wife had been at Beth Israel Hospital in Boston. That was her second hospital she had been to when she was taking CPT-11, which is one of the standard treatments that was not working. And the doctor there had a friend at Dana Farber, and he said, “I think there is a drug, oxily platin that they are giving out in compassionate use. We do not have it here at Beth Israel, but I think you should go to my friend, Dr. whatever, at Dana Farber and take it.” And the minute we got over to Dana Farber, they put her right on the oxily platin, and it was a compassionate use drug. We had never heard of compassionate use. We had never heard of oxily platin, but the doctors arranged it for her.

Then we got into the C225 and the other drugs, which we had to do all the work. I feel that it should be doctor to doctor, not me and a Web site or Mr. Burroughs or whoever, because we do not know what we are doing. We are wasting time. We are wasting money for the insurance company. The insurance company paid for my wife to go to Sloane Kettering to get all her information sent

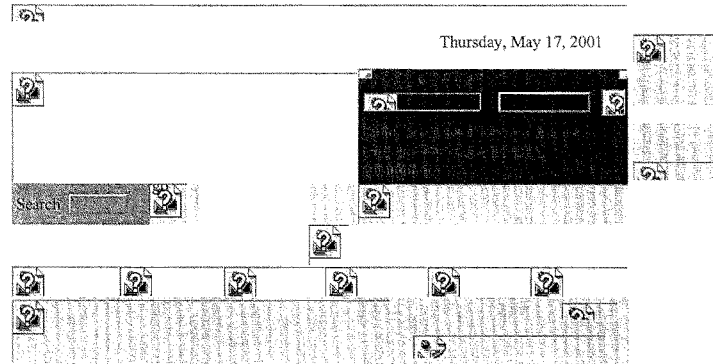
there and whatever. We never even used it. She died before. We did it on our own. We arranged to go to Sloane Kettering. I arranged other types of things on my own because I thought they were worth a try. But I guess I am questioning, why am I in the loop, why not a management person who is a medical doctor, just the way oxily platin worked? You know, I never heard of compassionate use. It did not matter. It was a treatment she needed, and the two doctors worked it out together, and that was—I think that is the moral for what I would propose. Everybody should know about it, and the doctors should have access to the information somehow, and take us out of the loop, really, because who knows if we are doing the right thing? And we are wasting money. We are wasting insurance companies' money. We are wasting time, and maybe we are not going to go down the right path.

So oxily platin was not even on a Web site anywhere when we got it, so it was the right thing. It worked for a while, but it did not work a long enough time for her, but she was able to get about 6 months of relief with the oxily platin, and that is my statement on it.

Mr. BURTON. Thank you, Mrs. Davis.

I really appreciate your testimony. Before you leave, I want to put some things in the record. I would like to submit into the record an article published in the "Boston Globe" by David Santino about his mother, and we will put that into the congressional record.

[The information referred to follows:]



May 16, 2001

Remembering mother's life, her fight against cancer

**By DAVE SANTINO**  
**GUEST COLUMNIST**

Longtime Thompson School teacher Ruth-Ann Santino died recently after battling cancer for more than two years. She left behind her husband, Fred, and two sons, David and Greg. I, David J. Santino, am her oldest son.

It is always saddening to hear of any highly-esteemed person in a community passing away. My mother was just that — a highly-esteemed person in the community. That it is evident by the number of people who came to her wake — almost 500. She was not admired because of flashiness or magnificence, but rather just because she was generally a good person.

Ruth-Ann Melloni, as she was named at birth, grew up in Somerville. She attended the St. Clement School from kindergarten through her senior year of high school, where she was a member of the varsity basketball team. From there, she attended Suffolk University, where she earned a bachelor's of arts degree in 1971. At Suffolk, she met my father, Fred Santino, and married him in 1974. After marrying, my parents moved to Arlington, where my family has lived ever since.

For years, my mother worked at the Boston Five Savings Bank, where she attained the position of vice president of human resources. My mother knew well that being vice president of a bank is a job that some people can only dream of doing. But in the early 1980s, two things made her decide to get out of the business.

The first thing was my birth in 1983. My mother could have stayed in her position after I

was born, but she would not hear of it. She wanted to be able to take care of my brother, Gregory, (who was born in 1985) and myself without worrying about the hassles that go with being vice president of a bank.

But my mother also left her position at the bank because she wanted to make more of a contribution to society. For this reason, she embarked on a teaching career.

In the mid-1980s, she started working as a substitute teacher in the Winchester Public School system. She later continued as a substitute in the Arlington Public School system.

She began attending Lesley College for a degree in education and soon after became a full-time teacher at the Thompson Elementary School, where she taught kindergarten, second grade, and third grade.

It truly gave my mother joy to teach. She was extremely well respected by her students because she had a unique way of connecting to them. This is no exaggeration. Any teacher or staff member at Thompson who knew her will agree with me. I actually saw her teaching methods myself several times when I visited her classes. She always had the ability to motivate children. She could take students who had done very poorly in school and turn them into more successful students. Perhaps, she acquired these teaching skills a few years back when she coached ice skating at the Bay State Ice Skating School.

It really hurt my mother, when she was teaching, to see children suffering because they had family problems. On one occasion I remember my mother being on the verge of tears while telling a story about a boy in her class who had informed her that his parents had not given him breakfast. Upon hearing this, she took the young boy out of school and bought him breakfast with money out of her own pocket. This is just one of many examples of how my mother was such a good person.

But Ruth-Ann Santino was not only a good teacher. She was also a fantastic mother who went above and beyond what was expected of her. Words cannot describe how good a mother she was.

She was the mother that all mothers should strive to be. She would wake up every morning to make sure my brother and I had all of our necessary items for the school day, and would constantly remind me with comments like, " Do you have your lunch? " or " Do you have your saxophone? "

My mother also always pushed Greg and I to be the best we could possibly be. But I think the greatest thing about her was that if we ever did fail, she was never angry or disappointed in us, as long as she knew we tried as hard as we could.

Even when she was sick with cancer, my mother would try her best to function in the mother role she had played throughout my life.

Over the summer, there were some days when she was in extreme pain and agony, but she still wanted all of us to go away to the beach or on vacation. She was a very strong-willed woman, who always thought of her children before she thought of herself.

Cancer is a disease that no one ever thinks will hit his or her family. So, if it does, the news always comes as an extreme shock.



I can still remember the day I was informed that my mother had been diagnosed with the terrible disease. It was a typical weeknight in March 1999, just a few days after my brother's 14th birthday and only four months before my parents' 25th wedding anniversary.

I was a sophomore in high school and my brother was in the eighth grade. As I was typing a book report on the book "Nothing To Prove: The Jim Abbott Story," my parents suddenly called my brother and I into our living room. I could already sense from the tones of their voices that something was amiss. We all sat down and my father started to do the talking.

My dad is usually a strong man, but this time he had trouble describing what the problem was. He told us that my mother would have to undergo an operation to remove a growth from her colon. I asked him what kind of a growth it was.

"It's like a pimple," he responded.

But I was not satisfied with my father's answer. I knew there was a deeper problem than what he had described. So I persisted in asking them to explain more of what was wrong with my mother. This time my mother responded herself and said only two words.

"It's cancer," she said.

The whole room was silent. I was stunned. My childhood feelings of immortality raced into my mind. How could my mother have cancer? Surely this could not happen to someone in my family.

A few weeks later, she underwent surgery at Mount Auburn Hospital to remove the cancerous tumor. The whole procedure seemed to run smoothly and all seemed well.

From May to August 1999, she underwent radiation and chemotherapy treatment, which really knocked out her system. She had countless side effects and was subsequently taken off the treatment. But in November 1999, it was discovered that my mother's cancer had reappeared.

This time, doctors took much more drastic measures and performed a colostomy surgery, which is a complete removal of the colon. The cancer was still in her system, however.

So, in February 2000, at Beth Israel Hospital, stints were inserted into her body and my mother underwent more chemotherapy. My mother would eventually end up having seven unsuccessful cancer treatments.

In July 2000, my parents were first informed that a drug in the clinical trial phase, called C-225, could save my mother's life because it takes a different approach than other treatments. The drug was not supposed to be available for a year, but in the fall, my parents actually heard that President Bill Clinton had sponsored a patient at Dana Farber Cancer Institute to be treated with the drug.

So, my mom and dad wrote three letters to the manufacturer of C-225, ImClone Systems, Inc., asking for compassionate use of the drug. Unfortunately, the letters were never

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answered.

My brother and I also wrote letters to ImClone, but those were not answered either. There was absolutely no response from ImClone until our family attorney and close friend, Alex L. Moschella, got involved in the situation.

He wrote letters himself to two ImClone officials. Just days before my mother's death, one of those men called my house and asked to speak to my dad.

Instead of apologizing for not responding to our letters or asking how my mother was, the official told my dad that we were being unfair to his company. My father was irate and so was the rest of family. My mother was dying at this point and ImClone had the nerve to say we were being unfair to their company.

In my opinion, that, along with failing to respond to a dying mother's plea, was completely unprofessional. My mother died two days later. A number of news outlets, like 60 Minutes, picked up on the story about ImClone's lack of compassion toward my mother's situation. My brother and I personally had the opportunity to vent our anger in an interview on WBZ-TV, which has helped us deal with the tragic loss of our mother.

I could go on forever attacking ImClone for their uncompassionate and unprofessional behavior, but that is not the purpose of this story. The main focus of this story is to celebrate the life of my mother, Ruth-Ann Santino. I hope I have done just that.

As I will graduate from Arlington High School in June and will attend Babson College in September, I know my mother would be proud of me if she was around. She was such a good mother that, although she lost the battle against cancer, I am sure that she will always be right by my side.

David Santino is a senior at Arlington High School.

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Mr. BURTON. I would also like to submit to the record a series of articles from the "Washington Post" on cancer issues, including one today about pediatric cancer patients not being given adequate end-of-life care.

And this comes in conjunction with one of my colleagues, Debra Price's daughter, who was treated for cancer, and had a terrible time with it.

And I have copies of statistics by State of cancer incidence and cancer mortality that I want to submit to the record.

And for anybody's information, in Indiana, it was estimated last year that 27,000 new cases of cancer were diagnosed, and 12,600 people died from it. And just you wonder how many could have been saved had they had a chance to have some compassionate use from these clinical trials.

In any event, God bless all of you. Thank you very much for being here. We really appreciate it. And hopefully because of your testimony and the testimony of others, we will come to some conclusion on how to deal with this problem. Thank you very much. Glad you made it. Thank you.

[The information referred to follows:]

**David Baxter, 16-year-old cancer patient needs your help**

David Baxter, age 16, of Woodland, CA is literally in a battle for his life. David was diagnosed with advanced stage-IV colorectal cancer in March 2001. David's oncology doctor wants to give him a promising new drug (C225) but the drug manufacturer won't let him give it to David. David's doctor already has this medicine that David needs and is already approved to use it for a head and neck cancer clinical trial at Sacramento's Sutter Cancer Center. The manufacturer, ImClone Systems Inc., has set up C225 clinical trials for colorectal cancer, but only on the East Coast. They said they would waive the 18 year old restriction but they want David to go back east for four months to get into one of these clinical trials. It is essential that David have the support of family and friends so this is a cruel requirement. It is also a needless request since David's doctor wants to participate in the same colorectal clinical trial, thus allowing David to get the drug. ImClone has refused to extend permission to David's doctor to use C225 to treat David's cancer—a treatment that could possibly allow David to live to see his high school graduation next year.

On 6/20/01, David's father will be testifying in Washington DC before the House Government Reform Committee about the problems families face in fighting drug companies to gain access to chemotherapy drugs that their doctors request.

To learn more about David Baxter and his experience with cancer please contact his father, Douglas Baxter at 530-668-9540 (h) or (530) 792-5811 (w), 871 Southwood, Woodland, CA 95695, Email: [baxter@ccio.com](mailto:baxter@ccio.com)




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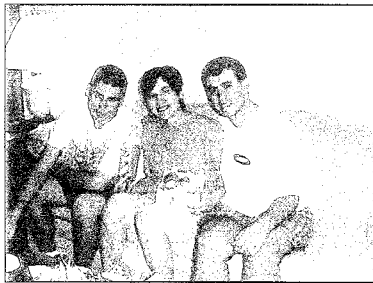
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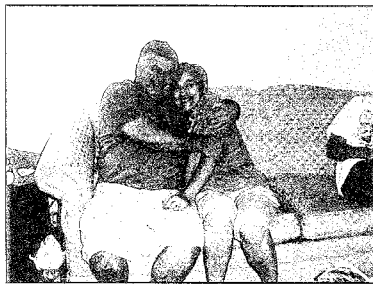
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Mr. BAXTER. Thank you.

Mr. BURTON. Our next panel will be Dr. Waksal, Dr. Temple, and Ms. Delaney. Would you please come forward?

If you could, would you please stand, so I can have you sworn?  
[Witnesses sworn.]

Mr. BURTON. Dr. Temple, do you have an opening statement?

Dr. TEMPLE. Yes, I do.

**STATEMENTS OF ROBERT J. TEMPLE, M.D., ASSOCIATE DIRECTOR FOR MEDICAL POLICY, CENTER FOR DRUG EVALUATION AND RESEARCH, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND PATRICIA C. DELANEY, PUBLIC HEALTH SPECIALIST, OFFICE OF SPECIAL HEALTH ISSUES, OFFICE OF INTERNATIONAL AND CONSTITUENT RELATIONS, OFFICE OF THE COMMISSIONER, FOOD AND DRUG ADMINISTRATION; AND SAMUEL D. WAKSAL, Ph.D., PRESIDENT AND CHIEF EXECUTIVE OFFICER, ImCLONE SYSTEMS, INC.**

Dr. TEMPLE. Mr. Chairman, members of the committee, I am Dr. Robert Temple. I am Associate Director for Medical Policy at the Center for Drug Evaluation and Research of FDA. I am also Director of the Office of Drug Evaluation I, which is where the Division of Oncology Drug Products resides.

With me today is Ms. Patricia Delaney from FDA's Office of Special Health Issues, the cancer liaison program, and I have submitted my full statement for the record.

I would like to highlight three main aspects of the use of investigational drugs to treat seriously ill patients, who have no satisfactory alternative, an arrangement sometimes called compassionate use, but that we call treatment use.

The first point I want to make is that FDA has, for many years, supported access to potentially useful drugs that are still under study. Since the 1970's, in fact, we have allowed, and even encouraged, treatment use of investigational—that is, drugs that are not approved yet—drugs.

Many believe this kind of availability began with AIDS, but in fact, we had allowed manufacturers of a number of kinds of drugs to make them very widely available before that, notably a kind of beta blocker for angina called cardio-selective, a wide range of new anti-arrhythmic drugs, and probably the largest of all, the calcium channel blocker, nifedipine, which was used to treat coronary artery spasm. Well over 20,000 people were treated with nifedipine before it was approved.

In all of these cases there was reasonably mature evidence of benefit and an acceptable safety record, and vigorous drug development efforts were going on.

In 1983 we proposed, and in 1987 formally promulgated, the treatment IND regulation, which was an effort to formalize pre-marketing availability of certain drugs that seemed particularly promising, and I want to mention several features of that rule.

It was explicitly intended to make promising new drugs available for treatment use as early in the drug development process as possible. It was expected, though, that availability would usually be relatively late in that process, in phase 3, except that it might be



earlier, during phase 2, for immediately life-threatening diseases, which cancer generally is. The rule requires the drug to be under active investigation by a sponsor who is actively pursuing marketing, and a treatment IND for a life-threatening illness must be based on a showing that the drug may be effective. That is the standard. The rule also requires that availability of the drug would not expose patients to unreasonable and significant additional risk. Thus, a certain amount of data is needed even to support early use under a treatment protocol.

FDA can stop an expanded access study if it is interfering with the conduct of the controlled trials of the drug. Sponsors who make drugs available under a treatment IND can recover costs once there is adequate enrollment in the controlled trials. Whether to offer a drug for use in a treatment protocol is solely within the discretion of its sponsor, although we sometimes suggest this pathway to the sponsor.

It was expected from the beginning that sponsors would make information about a treatment IND, about its existence, widely available to people, although we did not specify the ways that they would do that. In a treatment protocol access is usually open to any physician/patient combination that meets the protocol requirements, not just to selected patients or physicians identified by the company.

When we proposed the regulation in 1983, we were concerned that access to promising drugs had been available only to certain people who were "in the know," and we thought that if a drug was ready for this kind of use, any appropriate patient should have access and any appropriately qualified physician should be able to give the drug. We are aware that in some cases when supplies of drugs were limited, sponsors have used lotteries to choose among the people who had sought to get the drugs.

When we first began the process, we thought that all treatment use would be under treatment INDs, but that was probably unrealistic and has not proved to be true. Rather, a wide range of other kinds of requests for treatment use, especially treatment uses in specific individuals, which is sometimes called compassionate use, have emerged. Commercial sponsors are not required to agree to supply drug in those cases, but if they do, what is called a single-patient IND may come to us. In some cases a single-patient exception to the sponsor's ordinary protocol may be submitted to an existing IND. That is how many of these so-called compassionate uses occur.

Although we thought drugs would be available for treatment use only if there was a reasonable amount of data on safety and effectiveness, in oncology particularly, but in other cases too, critically ill patients and families sometimes seek treatments that have very little evidence supporting their value or safety, perhaps on the basis of animal studies or persuasive theories. As a general rule, unless there is a clearly better therapy for the patient, or clearly inadequate evidence of safety, our practice has been, and is, to allow these uses, at least in a modest number of a patients. But this is a matter that deserves careful scrutiny.

And that leads me to my second point, which is that allowing very early access to drugs, that is, access before there is really any

evidence at all that they work, is a very complicated matter and does not necessarily represent a benefit to patients. As patients run out of treatment options, some will search out a new treatment, every one not yet well tested. But we have experience with this. Typical early studies of new cancer drugs, are carved out in patients who have exhausted available therapy. It turns out that when the new agents are given to those patients, they are usually not very helpful, and significant responses are extremely unusual. Moreover, in most cancer chemotherapy trials, toxicity can be considerable, especially early, before approaches to managing toxicity are well established and before an appropriate dose is chosen.

It should also be appreciated that reasonable hypotheses do not always work out, as the current controversy over high-dose chemotherapy with bone marrow or stem cell research illustrates.

That said, I want to mention something that arose in the previous discussions. One of the things companies are sometimes asked to do is try a drug that is already being developed for one disease in treatment of a different tumor, perhaps in one or a small number of patients. Doing that is not unusual and actually resembles ordinary drug development. The proposed new use is like what is called a phase 2 study in cancer development parlance. And if a patient with a novel, a different tumor, such as a head and neck tumor, were to be incorporated into a study as a single patient for a drug that is being predominantly worked up for, say, lung cancer, that would not be a very unusual thing to do, and it would rarely give us any difficulty, even if there was not yet much information about the new use.

Because early access to drugs has both potential value and potentially serious risks, in December of last year and June of this year, FDA asked its Oncology Drugs Advisory Committee to consider when it is appropriate for FDA to allow investigational drugs to be used to treat individual cancer patients. The issue is obviously a complex one, but several speakers were surprisingly skeptical about individual patient use at very early stages. The statement of the National Breast Cancer Coalition [NBCC], for example, which I understand you have talked to, urged that access to investigational interventions outside of clinical trials be very limited, and expressed concern about unreasonable expectations created for women who have exhausted standard treatment. They feared that too-ready access would undermine clinical trials and the principle of evidence-based medicine, and might actually be harmful to patients.

The NBCC also thought that making access fair was very difficult, given practical and economic constraints. On the other hand, they strongly endorsed wide availability for patients not eligible for existing trials through a formal expanded access program when the therapy showed some effectiveness and low risk in phase 2 trials. They were very enthusiastic about the treatment IND.

They also urged that off-trial access, even at early stages, when it occurs, be in the form of an expanded access protocol, not through single-patient INDs. Many of the FDA's Oncology Drug Advisory Committee members expressed similar views.

Now, these are obviously complex and difficult issues that require balancing competing values and interests. We plan to hold a

broadly based workshop involving regulators, NCI academics, patient groups and individual patients to discuss these issues further. I believe, based on what I've heard today, we will also try to address formally the question of how to make information available about expanded access programs once they do exist.

The last point I want to emphasize, as others have today, is that fairness is extremely important. Any suggestion of unfairness in the way access to last-resort drugs is provided is extremely troublesome to everyone involved. It is becoming clear that any manufacturer with a drug that is arousing interest among patients and physicians should consider an organized program for providing whatever level of access it considers appropriate at a given stage of development. Access may have to be limited because of lack of data, insufficient drug supplies, or concern about use by physicians not experienced in how to use the drug. Or access may be more extensive, if that is supported by sufficient efficacy and safety data. But in any case, there ought to be a plan and people can find out what the plan is.

We have begun to urge companies developing cancer drugs to pay far more attention to this aspect of expanded access, and Ms. Delaney can tell you more about that later. For patients in search of treatment, a clear statement from sponsors as to what access is available is critical. Patients and family members have told us, time and time again, as they just told you, that they want clear answers. Even if the answer is no, knowing that answer sooner rather than later can allow patients to pursue other options.

That is the end of what I had prepared. I have a couple of comments in response to what I heard a little earlier, which I will do now if you like, or later.

One of the concerns people had was that companies might fear that data from access programs would contaminate their data and in some way impede approval of their application. I do not think, and I note Mr. Barr said this too, there is any real chance that would happen. We completely recognize that the efficacy data from an expanded access program is not the same as, or is to be mixed with, the efficacy data from an organized clinical trial. The expanded access patients have many reasons for being less responsive, and I do not believe anybody should have anxiety that we would confuse the two populations. It is true that if, in a wider access program, adverse effects were seen that had not been seen previously, we would want to know about those. But I think everybody would want to know about those. So I do not believe there should be a "fire wall" between those two kinds of studies. But I cannot think of a drug whose fate has been damaged by an adverse effect in an expanded access program. It could happen. Wider access, as we know, after drugs are marketed sometimes reveal things that we did not know from the smaller data base of drug development.

I guess the third point is that we do not just tolerate wider use of drugs prior to approval. I've already mentioned the treatment IND; in addition, we also actively support wider use prior to approval more generally. I used to call this phase 3½, and we used to try to get companies to, as they are getting their marketing application ready to submit to us, make the drug more widely avail-

able so that in fact there would be more safety and conceivably efficacy data available. So this is in no sense grudging. We think it is a good idea.

Finally, just briefly, the standards for approval of oncologic drugs are shaped unequivocally by the nature of the disease. The amount of data, the level of evidence that is required is usually far less than it would be for drugs for comparatively trivial illnesses. So we share the view that greater risks are acceptable for people who are facing the rigors of cancer.

Anyway, thank you, Mr. Chairman, and we will be glad to answer any questions.

[The prepared statement of Dr. Temple follows:]



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville MD 20857

STATEMENT BY

ROBERT J. TEMPLE, M.D.

ASSOCIATE DIRECTOR FOR MEDICAL POLICY  
CENTER FOR DRUG EVALUATION AND RESEARCH  
FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE  
COMMITTEE ON GOVERNMENT REFORM  
U.S. HOUSE OF REPRESENTATIVES

JUNE 20, 2001

RELEASE ONLY UPON DELIVERY

**Introduction**

Mr. Chairman, Members of the Committee, I am Robert Temple, M.D., Associate Director for Medical Policy, Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency). Also with me today is Ms. Patricia Delaney from FDA's Office of Special Health Issues (OSHI), Cancer Liaison Program.

**Background**

FDA would like to thank the Chairman for drawing attention to the important issue of the availability of investigational drugs for what is commonly referred to as compassionate use. First, let me say that while the phrase "compassionate use" is commonly used to describe some of the ways of making unapproved products available to patients, there is no FDA regulation or policy defining a "compassionate use." Compassion, an intent to help, should be, and is, an element of all drug investigation activities. In general, we describe these uses of drugs as "treatment uses," because their intent is to provide treatment of patients, not primarily to evaluate the safety and effectiveness of the drugs, the primary and usual purpose of studies under an Investigational New Drug Application (IND). FDA refers to compassionate use requests for individual patients as a "single patient IND" study, wider use would usually take place under a "treatment IND" or "treatment protocol" under an existing commercial IND.

We are very much aware of the impact FDA's processes and decisions have on the public we serve. Under the Federal Food, Drug, and Cosmetic (FD&C) Act and related statutes, the Government has a vitally important role in helping to ensure that the marketed

medical products upon which patients and their health care practitioners rely are shown to be both safe and effective. Just as important, we have critical responsibilities in helping to ensure that the use of investigational drugs is carried out safely, and that the limitations of current information on the drug is conveyed to the patient. We are particularly aware that even before a drug is approved for marketing, there may be enough information to support varying degrees of treatment use for people with serious illness when there is no effective treatment available. In various ways, FDA has attempted to make it possible for investigational drugs to be available in these situations, but availability must bear a relation to how much information we have. The safeguards provided by FDA's activities are particularly important for our most vulnerable citizens, those who are seriously ill.

We understand that patients and their family members are often unfamiliar with FDA's legal and regulatory responsibilities. Often they are unaware that FDA cannot compel a company to supply an individual patient with an investigational drug outside of its planned clinical trials. The manufacturer or sponsor makes the final decision to provide an experimental drug or therapy to a patient. The sponsor may consider many factors, including the amount of information available about the drug, the amount of drug available, and how best to use its resources to optimize development of the drug for marketing. This maximizes the availability of the drug to patients who can benefit from it. In some cases, the sponsor is unwilling to provide the product outside of clinical trials, especially relatively early in drug development. Patients are sometimes confused or angered by this situation and misinterpret the company's unwillingness to provide the product as an FDA action.

FDA may not allow treatment uses because of safety concerns. Generally, however, if a physician makes a request for treatment use of an experimental drug, in a patient for whom no effective therapy exists, and there is an ongoing study of the drug and a sponsor agrees to provide the product, FDA does not object to the treatment use.

There have been cases in which treatment use has been considered appropriate, despite relatively little evidence supporting the usefulness of the drug for the particular indication. Generally, when there was no effective alternative drug or treatment for the particular condition and there was sufficient information about safety, treatment use be justified. Physicians may always contact FDA to propose such a use for a specific patient when they believe circumstances warrant this use.

It is apparent that many manufacturers of promising drugs do not have standard operating procedures in place for handling requests for single patient INDs, especially when the promise of the drug is just becoming appreciated. This has created confusion and, in some cases, led to perceptions of an unfair system, in which some people can gain access to therapies while others, who appear similarly situated, cannot. The patients seeking these drugs are frequently cancer patients who have exhausted standard treatment. They, and their relatives, are often desperately seeking a last chance to prolong their lives. Any impediment to obtaining the drugs would be most unwelcome. Actual or perceived unfairness would seem intolerable.



**Recent FDA Activities on Access**

FDA is generally satisfied with how the current system of access to INDs and single patient INDs is working, but there are problems and some inherent limitations of the system. We realize that the experience of some individuals has not been satisfactory and has seemed unfair and there is a public perception of a very convoluted system to gain access to these drugs.

Let me bring you up to date on some recent FDA activities that have addressed issues of access to experimental drugs and single patient INDs.

At the December 13 and 14, 2000, and the June 7, 2001, Oncologic Drugs Advisory Committee (ODAC) meetings, FDA solicited advice from the committee on when it is appropriate for FDA to allow investigational drugs to be used for treatment of individual cancer patients. An important additional objective of the meeting was to educate the public, physicians, and ODAC on the issues surrounding access to investigational cancer drugs for single patient treatment use.

The individual presentations and discussions at the meeting were wide-ranging, very thoughtful and, it is fair to say, somewhat surprising. These were patients or relatives of patients who spoke feelingly of their difficulties and frustrations in seeking potentially useful treatment for cancers that had not responded to other therapy. A number of patient groups spoke with equal feeling on the need to develop treatment rationally, to defer treatment use until adequate information supports it (and only then to make it available)

and to correct the widespread misimpression that there are magic bullets available for treatment of refractory malignancies. They also emphasized the need for widely available information about drugs under study and those drugs for which more widespread availability was appropriate and available. It was clear that the overall situation was one of great complexity, but these groups did not believe that wide use of toxic drugs without known benefit was a service to seriously ill patients.

### **Industry Concerns About Treatment use of Investigational Drugs**

Commercial sponsors are not always willing to supply drug for treatment uses. A number of industry concerns about the use of experimental drugs were discussed at the June 7, 2001, ODAC meeting.

- (1) There may be a limited drug supply early in drug development. The batches prepared for early drug studies are usually small; making larger amounts available is expensive and not considered reasonable until there begins to be evidence that the drug is of value.
- (2) There may be competition between expanded access programs and the regulatory programs that will lead to drug approval. Competition can be either for patients entering trials or for internal company resources. The process of individualized packing and shipping of drugs for single patient use on an emergent basis can be very disruptive to departments that are organized to pack and ship drugs in a scheduled manner for clinical trials. There is significant concern that availability of all investigational drugs outside a formal protocol will decrease participation in the formal study. In fact, FDA rules allow open studies to be put on hold if they are interfering with the conduct of clinical trials.
- (3) The use of an investigational drug in less controlled setting, in patients with very advanced disease could lead to adverse reactions that might raise difficult to resolve but spurious safety concerns about the drug.
- (4) Industry seems to learn little about a drug from single patient use. FDA expects very low response rates in patients who have received multiple previous therapies and a low rate in such patients would not damage the drug's chance for approval.

At the conclusion of the meeting, it was obvious that this issue deserved further discussion and exchange of views. FDA has suggested that a consensus development meeting be convened in the near future, involving industry, academia, patient advocacy groups and regulators to discuss these issues. FDA and the National Cancer Institute could play an important role in organizing and facilitating the conference. We will be glad to provide the committee with the written statements offered at the ODAC meeting and a transcript of the June 7, 2001, discussions.

### **Current Access Procedures**

We would like to clarify FDA's role in making INDs available for treatment uses. First, to put the subject into context, I would like to briefly address the public health system of getting unapproved drugs to patients.

### **Clinical Trials**

FDA's primary obligations are those vested in us by Congress in the FD&C Act and the Public Health Service Act, that ensure that marketed medical products are, safe, effective, properly labeled and that experimental drug studies are designed to protect the patient volunteers.

Before being approved by FDA for marketing, new drugs and biological products must be proven effective in controlled clinical trials and shown to be safe. FDA is directed, under the FD&C Act, to rely on evidence of effectiveness based upon adequate and well-controlled studies. The persons who participate in any trials under an IND must be fully

informed of the risks and possible benefits of their participation and studies must be designed to adequately protect the patients from harm. Patients must be informed about alternative medical treatments, whether approved or investigational. This is possible only when there is adequate pre-clinical data from animal studies or from other sources to provide the information upon which informed consent can be based.

### **Access to a Clinical Trial**

The access process starts with a drug sponsor, a pharmaceutical company or a research scientist at a university or at the National Institutes of Health (NIH), seeking to develop a new drug. Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals (pre-clinical studies). If the laboratory and animal study results show promise, the sponsor must submit an IND to FDA for review before beginning a trial in people.

After a study passes FDA review and a local Institutional Review Board (IRB) (a panel of scientists and non-scientists that oversees clinical research) approves the protocol for clinical trials, experienced clinical investigators give the drug to a small number of patients. These Phase I studies are designed to assess the most common acute adverse effects and examine the amount of drug that patients can take safely without unacceptable side effects. It is unusual in this setting to see important patient benefits. Initial clinical studies are also designed to better understand what happens to a drug in the human body, how it is changed (metabolized), how much of it (or a metabolite) gets into the blood and

various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If Phase I studies do not reveal major problems, such as unacceptable toxicity, Phase II studies are conducted to determine the effectiveness of the drug in patients who have the medical condition that is intended to be affected by the drug. Researchers then assess whether the drug has a favorable effect, for example, in cancer patients by seeing whether the tumor size is reduced.

In some cases the Phase II studies reveal results so impressive that these studies alone are the basis for approval, generally for treatment of refractory disease. This is often done under FDA's accelerated approval rule (similar to the fast-track provision under FDA's Modernization Act of 1997 [FDAMA]) which allows FDA to approve drugs on the basis of a surrogate endpoint (effect on a measurement such as a tumor size likely to lead to a real patient improvement) on condition that post-marketing studies demonstrate a tangible patient benefit. In most cases, if Phase II studies show desirable responses, Phase III studies are conducted. Those are concurrently controlled studies in which two therapies are compared. These usually are 1) a comparison of standard treatment alone, or 2) a comparison of the new treatment alone with an older treatment to show that the new treatment is not worse than the older treatment or is its superior.

It is generally believed that it would be in everyone's interest if more patients participated in trials of new cancer treatments. We recommend that anyone interested in participating

in a clinical trial discuss the idea with his or her physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Detailed information can be obtained from a variety of sources, including drug sponsors, FDA (if the information is public), a new website [www.clinicaltrials.gov](http://www.clinicaltrials.gov), and NIH. Clinical trials are carried out at major medical research centers such as teaching hospitals, at NIH, and even in doctors' offices. Although they often involve hospitalized patients, many clinical trials can be conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper ads recruiting potential participants for clinical studies that tell readers where to call or write for further information.

The full implications of taking part in a clinical trial must be fully explained to potential patient subjects in advance by the people conducting the trial and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug, or the desire to take part in research that might one-day benefit millions, is what makes people volunteer for clinical trials. These hopes and desires should not prevent them, however, from finding out all they can about being a part of the process. Many seemingly promising agents prove not to be helpful or too toxic to use and, especially in early trials, major benefits are clearly the exception.

**Protocol Exception/Exemptions**

In cases where a patient cannot be enrolled in an existing protocol because of some factor that makes the patient ineligible to participate in the study, research sponsors or investigators often can make a protocol exception to treat such a patient. The data from that patient would not be part of the report of the original study. Usually such special exceptions arise in the same institutions that are conducting the original study, where investigators are familiar with the drug.

**Access to Investigational New Products**

The ideal way for a patient to receive a promising but unproven drug is as a participant in a controlled clinical trial. Such trials provide appropriate patient protections and potential benefits (for example, IRB review, informed consent, free product or treatment, and FDA review of pre-clinical data and the protocols for the clinical trials) and maximize the gathering of useful information about the product, potentially benefiting the entire patient population. It is not possible, however, for all patients who might benefit from the drug to enroll in controlled clinical trials.

FDA believes that it is appropriate to make certain promising, but not yet approved, products available to patients with serious and life-threatening illnesses who lack alternative treatment. This should be done in a way that does not interfere with recruitment to the clinical trials needed to support the effectiveness and safety of the drug. It should also be done fairly. A major goal of the treatment IND proposed in 1982, and made final in 1987, was to make unapproved but promising drugs with appropriate

evidence of effectiveness widely available prior to marketing. In the past such drugs often had been available but only at selected sites.

### **Single Patient INDs**

The paperwork reporting responsibilities a sponsor must submit for a single patient IND or single patient use under an existing IND is modest. If a patient is treated under an existing IND, the sponsor must collect and report adverse reactions and include such events in its annual reports. A single investigator wanting to treat a patient will refer to the commercial IND for most information and will have to provide additional information about the patient to be treated to obtain informed consent and local IRB approval. Exactly what to do is described in the oncology part of FDA's website and the Agency's role in the process [www.fda.gov/cder/cancer/single IND.html](http://www.fda.gov/cder/cancer/single%20IND.html).

### **FDA's role in the process**

One may ask why FDA is involved in this process at all. That is, why should not the physician and patient decide on the appropriateness of treatment? We believe that the independent scientific consideration provided by the Agency is critical and is an essential component of patient protection, when one is considering drugs about which relatively little is often known and especially when potential toxicity is great. In the typical single patient IND situation, especially those involving emergency IND requests, the patient's physician generally has only very limited information about the investigational therapy being requested.



FDA has set up internal procedures to facilitate single patient IND requests. Physicians are put in touch with a Consumer Safety Officer (CSO) within the relevant reviewing division; the CSO helps the physician understand the IND process to facilitate completion of the IND application.

### **Progress Since FDAMA**

Section 402 of FDAMA codified certain FDA regulations and practices regarding expanded patient access to experimental drugs and devices. FDAMA addresses three expanded access procedures with respect to: 1) emergency situations; 2) individual patient access to investigational products intended for serious diseases; and 3) treatment IND applications and treatment investigational device exemptions (IDE). The Agency continues to review current regulations and practices in light of FDAMA and is currently developing new regulations to codify current practices. FDAMA continues to emphasize for all those cases, including individual uses that the appropriateness of expanded access depends on available data, i.e., “sufficient evidence of safety and effectiveness to support the [proposed] use.”

For the past four years, Agency efforts have included: 1) expediting approval of cancer therapies; 2) encouraging new uses of marketed products in cancer treatment; 3) expanding access to investigational cancer therapies that have been approved in other countries; and 4) appointing cancer patients to our Oncologic Drug Advisory Committee, which reviews new cancer therapies.

### **Expediting Development, Review, and Approval of New Products**

An important means of providing access to new cancer therapy is the rapid development and approval of new agents. FDA has implemented mechanisms designed to increase access to new drugs and biologics by expediting their development, review and approval. All of these programs have been instrumental in shortening the time to marketing approval for cancer drugs and biologics. FDA programs include:

- Expedited development under Title 21, Code of Federal Regulations (CFR) Part 312, Subpart E expedites the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely debilitating illnesses.
- Priority Review to speed the review of NDAs, biologics license applications (BLAs), and effectiveness supplements that could have important therapeutic impacts. The standard review time of ten months. Since 1996, five biologics and 31 drugs (20 NDAs and 11 supplements) for cancer therapies have received priority review and approval.
- Fast Track section 112 of FDAMA, amends the FD&C Act to consolidate the various provisions intended to facilitate the investigational development and approval of drugs and biologics that provide significant advances in the treatment of serious diseases. This codified FDA's accelerated approval regulations. Perhaps the most important, yet under appreciated aspect of fast track is FDA's commitment to work closely with sponsors throughout the drug development process to agree on study designs and appropriate outcome measures, etc. This allows companies to plan and carry out the most rapid possible responsible development. FDA meets constantly with sponsors taking advantage of this opportunity.

FDA's overall goal is to improve significantly patient access to promising cancer treatments and treatments for other life-threatening illnesses without compromising patient safety. When we do this we seek optimal development and use pre-marketing access when this is safe and appropriate. Importantly, FDA regulations emphasize safeguards for the protection of human subjects, including the requirement for informed consent.

**The Office of Special Health Issues**

FDA is mindful of the frustrations that patients with life threatening illnesses and their families experience when trying to obtain information about potentially helpful therapies, especially when there is no standard therapy. In addition to offices within FDA's Center for Biologics Evaluation and Research and CDER that routinely provide assistance and information to consumers, OSHI provides information and works with cancer patients and their advocates on cancer-related issues. Most activity in OSHI is on behalf of patients with life threatening diseases, most often cancer and AIDS.

Usually, callers want information about treatments currently being researched. Although we cannot disclose proprietary information about products under development, we are able to talk with patients about any treatment that appears in public access databases.

In response to Section 113 of FDAMA, FDA has worked with NIH to develop a data bank of clinical trials of therapies for serious or life-threatening diseases. The data bank, [www.clinicaltrials.gov](http://www.clinicaltrials.gov), currently lists over 5000 trials sponsored by NIH, other Federal agencies, universities, and the pharmaceutical industry. We anticipate that many more industry trials will be included after the final guidance document is available.

Our goals in serving patients with life-threatening diseases and their family members are straightforward:

- (1) Promptness (returning patients' and family members' calls within 24 hours);

- (2) Accessibility (listening to the caller's concerns and giving him or her as much time as he or she needs);
- (3) Education (about the drug approval process and his or her options); and
- (4) Assistance (providing additional information to the patient or family member that may be helpful, e.g. other sources of information).

### **Conclusion**

Even as they provide high standards and protection of patients, the laws and regulations are flexible and allow patients with no alternatives access to promising, but not yet unapproved treatments while preserving the system of well-controlled clinical trials that provides the information necessary to determine the safety and effectiveness of proposed new products.

Protection of public health, compassion and respect for individuals, can, and do, co-exist.

Thank you for the opportunity to testify. I will be happy to answer any questions the Committee might have.

Mr. BURTON. Thank you, Dr. Temple.

Ms. Delaney, do you have an opening statement?

Ms. DELANEY. I do not have formal remarks, but I am available for questions.

Mr. BURTON. OK. Dr. Waksal.

Dr. WAKSAL. Good afternoon. Thank you.

Mr. Chairman, my name is Dr. Samuel Waksal, and I am the president and chief executive officer of ImClone Systems. I appreciate the opportunity to testify before the committee this afternoon.

Before I go on with the rest of my testimony, I just want to briefly interrupt and say that is a very difficult situation to ever deal with with patients, with family members of patients who have cancer and our sincere—and our hearts go out to these patients. There is no answer to give to husbands and fathers and other family members of patients who have died of cancer. And this is not meant as a rebuttal to anyone. We are here to talk about what we are trying to do in the same way that this committee interests allies, in looking forward to figuring out how to best deal with this very difficult disease, and we share this committee's goal and a commitment to all of that. In fact, ImClone scientists have spent the greater part of their careers moving forward and trying to discover these new approaches to the treatment of cancer that we hope will change the way cancer is treated in this next millennium.

I want to discuss today our experience with the treatment IND or compassionate use IND that we have been talking about, and our experience is with the development of our first therapeutic agent, IMC-C225, and I hope that what we tell you here today will help this committee look at the very difficult issues that we are talking about.

We are currently going through the FDA approval process to get IMC-C225 approved and out into the market, and we have been testing this drug in patients now since January 1995. We have been looking at a variety of cancers. We have been using IMC-C225 in the area of head and neck cancer, in colorectal cancer, in pancreatic cancer and lung cancer. And in May 2000 we had data that was presented at the American Society for Clinical Oncology that showed great promise for this drug in colorectal cancer and head and neck cancer in patients who had failed conventional chemotherapy, and there was a lot of media attention at that time on our drug because of the results that were presented.

Because of all of that we had really an onslaught of requests for compassionate use protocols for IMC-C225, and we have been moving forward and completed, in effect, this last year, our phase II studies for the use of our drug in colorectal cancer in patients who had failed conventional therapies. The FDA has given us fast-track designation to move this forward, and we expect to move it forward with a biologics license application very soon.

For us the critical issue has not been money. For us the critical issue is not that we are afraid of contaminating our clinical trials, and in fact are moving forward with our clinical trials, and believe that our first obligation, obviously, is to prove that this drug is safe and is effective in standard clinical protocols that we put together in conjunction with the FDA.

For us the critical issue has been manufacturing. This is a biologic. It is a protein-based drug. Unlike small molecules that most pharmaceutical companies developed and are developing of the kind that AstraZenica or OSI Pharmaceuticals make, this is a protein-based drug that has very stringent biologic manufacturing standards. And in effect, we are so committed, that early on, before we really knew that this drug was going to have any activity, when it was still in preclinical studies, we built a pilot manufacturing facility that would allow us to move forward in clinical trials, and we did that back in 1994. Moreover, at the present time, we only have enough clinical supply to give us about 10 weeks of additional therapy for each of the patients on our clinical protocols.

Also we have a contract manufacturer that we have gone out to find because we are living in a world right now where there is not enough manufacturing capacity for these types of protein-based drugs, and there has been a lot of news about that over the past several months. So, in effect, we do have a contract with a third-party manufacturer, and again, money has not been an issue. We have requested every single run that they might have in their facility to make our product and are doing that as we move forward. However, this supply is limited and our obligation and the obligation to the future of—to future cancer patients is to move forward through clinical trials, prove that the drug is safe and effective, and get it on the market.

Prior to May 2000, when very few people who knew about this drug, the only compassionate use requests that we got were from clinicians that were in our clinical trials and had experience with our drug. Between January 1995 and May 2000, we had very few compassionate use requests, and we put 15 patients on compassionate use protocols up until May 2000. After May 2000 and until January of this year, when we ended our compassionate use program, we treated an additional 15 people. But the requests were very different. Instead of physicians that really knew how to use this drug and knew about the drug, it was more the media and a lot of word-of-mouth because of clinical data that was being presented at conferences that really drove a huge amount of these types of requests, and as we put into our testimony, we have had almost 10,000 requests for this drug, about 8,000 different patients that have requested IMC-C225 for various types of cancers, and this has been a very difficult thing for us because as compassionate as we are, we are a small biotech company, not a big pharmaceutical company, and it is very difficult to process that kind of request, those kinds of requests by this many patients.

Initially what we did was really try to set up a hotline right after May 2000 to deal with some of these requests, and we really feel badly. We probably should have put a form letter together. We were unexperienced at the time, and the data that we had generated was really new to us at that point, and in effect, perhaps we should have put a form letter together to get back to these patients to tell them that there were limited amounts of slots available for these compassionate use programs. Indeed, what we initially put together was a list of first come-first serve, and when that got too big and we were afraid that we were going to give false hope to anybody that even got on the list, we finally ended our pro-

gram and decided to concentrate on getting the drug approved because we felt that was the best way to get this drug out to as many people as possible in an approved fashion.

So after having to turn away all these people, we are now concentrating on a couple of things. One, is we have, even before we had the further data that our drug was working in colorectal cancer in the refractory setting in patients who had failed conventional therapies, and in the setting of head and neck cancer, in January 2000 we broke ground on a very large manufacturing facility. So we took that huge risk ourselves. No one helped us. We were not partnering this drug with a big pharmaceutical company at the time, and we took the risk to make sure that a major facility could be built that would make this drug available to cancer patients in the future. We just completed the physical completion of that facility in record time, I might say, and now we are beginning to get ready to make it in that facility, under very strict FDA guidelines, so that facility can later be approved and we can have material available for patients after the drug is approved, and also to revisit how we would put together an expanded access program for even more patients.

So would we do things differently in the future or would we have done things differently in the past? The answer is yes. We were a very young and inexperienced company, concentrating on putting together and discovering new novel therapeutics for the future treatment of cancer that were different than the kinds of therapies that had been discovered in the past, and we are happy to say that we, as pioneers in that area, have pioneered a new approach of targeted oncology to get these new kinds of drugs out there. We are in the last stages of dealing with the FDA and moving forward in conjunction with the FDA to try to get this product approved, and at the same time, expending our meager resources—and they are far less than big pharmaceutical companies—but expending all the moneys that we can to make sure that we have the manufacturing capability available, to have drug availability for these individuals, and to do everything we can to treat disease that are heart wrenching in every individual aspect. And what we are trying to do is get out there and serve the thousands of patients in the future that need our drug.

Thank you, Mr. Chairman.

[The prepared statement of Dr. Waksal follows:]

Testimony of Dr. Samuel Waksal  
President and CEO  
ImClone Systems Incorporated

Before the  
House Committee on Government Reform

June 20, 2001



Good afternoon. My name is Dr. Samuel Waksal and I am the President and Chief Executive Officer of ImClone Systems Incorporated. I appreciate the opportunity to testify before the Committee this afternoon on the important subject of compassionate use INDs. I want to commend the Committee for its interest in the question of how we can get better treatments for cancer to more patients more quickly, which has always been ImClone Systems' goal. Today, I want to discuss our experience with compassionate use during the development of our therapeutic candidate for cancer, IMC-C225, with the hope that our story may provide insight into the challenges and promise of compassionate use programs.

ImClone Systems is a publicly traded biotechnology company with offices and laboratories in New York City and manufacturing facilities in Somerville, New Jersey. Our key focus is research and development of novel therapeutic agents for the treatment of cancer. Our scientists have spent the better part of their careers doing research in the field of oncology. They are committed to the discovery of a new generation of drugs to help change how cancer will be treated in the future. ImClone Systems is currently seeking FDA approval of IMC-C225, which is our company's first drug to have reached cancer patients. We at the company have been working on IMC-C225 since the early 1990s and have been performing clinical trials with it since 1995. We have been working closely with the FDA to prepare for filing for approval of the drug in a particular cancer indication, and we will continue to work with them in the future based on our ongoing trial data to seek to have the drug approved for additional indications. We are a

small company. With less than 100 employees in the early days of IMC-C225 trials, we have now grown to just over 300 employees. IMC-C225 and our other therapeutic candidates for various cancer indications represent years of hard work by employees and others committed to making sure this drug gets to patients who might benefit from it.

IMC-C225 has been tested by ImClone Systems in association with leading clinical investigators over the past five years in patients with several different types of solid tumors, including patients with colorectal cancer, head and neck cancer, and lung and pancreatic cancers. These clinical trials have yielded the data that we are required to submit to the FDA in our application for approval for use of the drug. In the past year, IMC-C225 has received increasing notoriety based on clinical results that have been released to the public. This information has largely come from publications on IMC-C225 by investigators in academic journals and at scientific meetings. In May 2000, at the American Society of Clinical Oncology in New Orleans, publications were made by principal investigators who headed our various trials. The published results demonstrated that the drug had a significant effect on certain cancer patient populations, namely patients with colorectal and head and neck cancers whose tumors had continued to grow after treatment with standard therapies. These are so-called "refractory" patients. As a result of widespread publicity surrounding these favorable results, there has been a great deal of interest in gaining access to IMC-C225. This interest has been further spurred by additional data that was presented at this year's ASCO meeting held last month in San Francisco, where further positive data was disclosed of the ability of the drug to work in various patient populations, including those with refractory colorectal cancer, refractory head and neck cancer, and pancreatic cancer.

In considering and implementing its compassionate use program, our company has been constrained by limitations on availability of drug material for the conduct of its clinical trials. At this point IMC-C225 has been tested in more than 700 patients over a five year period, of which 30 have been compassionate use patients. Most of the more than 700 patients have been treated with IMC-C225 manufactured by us. To manufacture this biologic product in accordance with FDA guidelines is an accomplishment in and of itself. IMC-C225 is a protein, not a small molecule chemical entity like more traditional pharmaceuticals. It is derived from a living cell line that has been created to produce it. The conditions and the various steps under which it is made are closely controlled, numerous and very expensive. Under strict FDA guidelines, each step must be thoroughly documented and that documentation must be made available to the FDA before the material can be administered to patients.

There is at present a paucity of biologic manufacturing capacity in the world. Our company responded to this challenge early on by taking the step of building and outfitting its own clinical trial manufacturing facility in order to meet the needs of FDA testing. We have also contracted with outside groups that can make this kind of material. We have taken these steps to ensure that we would have enough material to conduct the kinds of trials that might result in the data that we can present to the FDA for approval of IMC-C225. We have also been mindful of the need to make more of the drug as our positive data has come in, and we have therefore built an additional, larger manufacturing facility in order to expand our supply. We have made great effort to build this facility in an accelerated fashion, and we will begin making material in it shortly. This is an enormous achievement for any biopharmaceutical company, and particularly

for a small company like ours. We are doing this so that we can have enough IMC-C225 to meet the needs of the patient population in anticipation of FDA approval.

Drug supply is a very significant issue for these kinds of products, during the testing phase and thereafter. We have planned and built capacity to address this issue, and we continue to take the steps to ensure that there will be adequate supply if and when the market expands. During the testing phase we have sought to carefully husband the drug that we have had available from our manufacturing efforts and those of our suppliers, and to maximize the benefit of this limited supply in appropriately designed clinical trials. These trials are designed to demonstrate the endpoints that we have agreed with the FDA must be met in order for this drug to be approved.

As we have collected the data from our trials and from our earlier research, we have been working very closely with the FDA in order to prepare the Biologic License Application that we are filing. Fortunately, the FDA has procedures in place that permit it to direct special attention to a drug candidate that may meet an unmet medical need. Using expedited procedures created by Congress, the FDA has put our development program for IMC-C225 for the treatment of refractory colorectal cancer on a “fast track,” the effect of which is that they will continue to work closely with us to receive and examine the data as we supply it, in order to expedite the approval process.

From the time that ImClone Systems began testing IMC-C225 in people, there have been requests from the community for the compassionate use of the drug. As you know,

compassionate use INDs are essentially applications to the FDA to use a drug like IMC-C225 outside of the regular clinical trials that the company has designed and conducts in order to develop the safety and efficacy data necessary to be presented to the FDA for approval. Typically, applicants are patients who have not been able to participate in one of the company's clinical trials because the patient does not fit the eligibility criteria for that trial. The patient, for instance, may be too young, too ill, or may have been given therapies that are inconsistent with the trial protocol.

Out of the over 700 patients that have been treated with IMC-C225 by ImClone Systems in its trials, 30 have been treated through compassionate use. Early on, before the publicity surrounding the drug, compassionate use patients would generally be chosen in the following way. Oncologists who knew of the drug or had worked with the company or with one of the institutions that was studying the drug, would come to the company's clinical group with a particular patient history and need. The company and the clinician would then discuss this particular case, including what might be learned from such an individual study. ImClone Systems valued these early requests because they offered the possibility of investigating new indications during the early period of our clinical experience with the drug. And in fact there were cases where much was learned. For example the first patient with refractory colorectal cancer that was treated with IMC-C225, who is here today, was treated on compassionate use. The patient's physician had done research with IMC-C225 in pre-clinical models of colorectal cancer. Understanding the drug and its potential mechanism, her doctor came to us with the request that he be able to have it to treat this patient. Fortunately, the drug has shown positive results.

Reporting of these results contributed to the media attention to IMC-C225. Later, as publicity on the drug grew, following publication in scientific journals and at conferences of the early results with the drug in this patient population in particular, a large number of requests for access to the drug outside of our trials began to come to the company. We established by contract a call center, staffed by nurse practitioners, to field requests and give inquirers information about our studies and about other studies that might be available elsewhere. Those who wished to speak further about the possibility of receiving the drug were referred directly to our medical director. From May 2000, the first date of significant publicity, until January 2001, when we ended the compassionate use program, there were over 8,500 requests for participation in our clinical trials or compassionate use protocols. Our medical director spoke directly to more than 500 of these patients or their family members or doctors. We established a list in order to attempt to give access on a first come first served basis. Within months the list had more people than we could possibly serve with drug that we had dedicated for such compassionate use access, so we stopped adding names to the list. We felt that to tell someone that we were including their name would be to unfairly hold out false hope that he or she might be able to get the drug. We tried hard to keep to the first come first served basis, but this was extremely difficult. We received many emotional pleas from patients, their families and their supporters. Some would have special appeal because of the age or situation of the applicant, or because of the familiarity of their oncologist with use of the drug and with other trials that the company was conducting. You can imagine how difficult a process this would be for any company, of whatever size, but particularly for a small company that had never experienced this before, had little guidance as to how to conduct itself in such a situation, and had extremely limited drug supply. It was very

difficult to make these decisions, and to know that we could serve so few of these needy patients. For each person to whom we said yes, there were so many to whom we had to say no. This was an enormously painful process for our company.

We have learned much from this experience, certainly that we were naive at the outset to think that we could handle such a situation without great difficulty. Nevertheless we sought to be responsive simply because all agreed that it was the right thing to do. But eventually we were overwhelmed with the burden of having so little drug supply that we could dedicate to so many heart-wrenching requests -- requests that we knew in almost all cases we could not fill -- and we decided that the best thing we could do was to stop the program, which we did in January of this year.

In the end, out of a total of 149 refractory colorectal patients that have been treated to date with IMC-C225, 11 were treated on compassionate use. This is over 7 percent. And of 700 total patients treated with IMC-C225, 30 have been treated on compassionate use. That is over 4 percent.

Could there be a better system to determine who should be treated? Our experience has taught us that there is. Yet, at the same time when you field 8,500 requests and have only 30 spots, any system will be deemed to be inherently unfair. That certainly is the case for those who didn't get the drug, and our hearts have gone out to each and every one of them. We know we have let people down, but we have tried to do our best. Our feeling has been and continues to be that the best and most compassionate thing we can do now is to concentrate on getting the drug

approved as expeditiously and as broadly as possible, so that all the patients in need can get this drug.

One of our highest priorities is to greatly increase the supply of IMC-C225. We have completed construction of our own large-scale biologic production facility, which will be dedicated to production of IMC-C225. Once that facility is producing material, we will consider once again instituting a compassionate use IND program or, if we are at the appropriate stage of the approval process, an even larger "Expanded Access" program. The size and particulars of such a program would depend on factors such as the supply of IMC-C225 available and the demands of our ongoing clinical development program, including post-approval. If we are able to undertake such a program, we intend to use the lessons learned from our previous experience in designing and administering the program.

We will also continue to conduct clinical trials in additional indications and in expanded populations within those indications. As a drug is proven safe and effective in the sickest populations, less sick populations can then be tested. Ultimately we feel that the most compassionate way for us to proceed as a company with a potentially significant new therapeutic treatment for cancer is to continue to develop it as expeditiously as possible through the conduct of scientifically sound clinical studies. This we believe will optimize the potential benefit that IMC-C225 can offer.

Are there things that can be done to the system that could improve upon this difficult situation? We feel that there are. First, the choices that must be made by a company in our



situation – whether or not to have a compassionate use program and to what extent to dedicate drug supply to this program – should of course remain voluntary, as they are now. However, if a company chooses, as we did, to have such a program, the decisions that it must make as to who gets the drug and who does not is a burden that could somehow be shifted from the company. Once a company makes a decision to dedicate a certain amount of its drug supply to compassionate use, then within these limitations, assistance in administering the program could come from a responsible third party. The National Cancer Institute comes to mind as a group that would be well prepared to take on this role. Naturally the company would need to preserve flexibility in terms of how much material from time to time they could dedicate to such use, but the tremendous human task of making these kinds of difficult decisions could be shifted to a group better prepared to deal with making these kinds of determinations.

In addition, we have talked about the lack of companies that can manufacture biologic product. To the extent that the industry can be further incentivized and encouraged in such a way that this capacity would increase, this would be a boon to companies, especially small ones, that are researching and developing biologic products.

Once again, I commend the Committee for convening this hearing. I appreciate the opportunity to appear before you and I look forward to answering your questions.

Mr. BURTON. Thank you, doctor.

Dr. Temple, Ms. Delaney, given the information that Dr. Waksal just gave us, how long would it take from this point on to have the C225 approved and ready for dissemination to the populace? They started the clinical trials, I guess, in 1995; is that what you said?

Dr. WAKSAL. Yes. We started clinical trials in 1995, but—

Mr. BURTON. So in 1995. Now we are 6 years into it, and it is showing some promise, and, you know, having 130,000 cases of colorectal cancer this year, and every one of those people, knowing that it has some positive results, would probably like to have this product. So how long does it take the FDA to get that done?

Dr. TEMPLE. Well, I cannot speak about that biologic for a number of reasons. For one thing it is reviewed in a different center.

Mr. BURTON. Wait a minute. Excuse me. It is in a different center? I thought when—we wanted FDA to send some people up here that were familiar with this particular product.

Dr. TEMPLE. Well, this may be a terrible error on our part, and if so, I am sorry, but the request to us—

Mr. BURTON. You mean there is nobody here from FDA that can tell us anything about—

Dr. TEMPLE. About this drug? That is, I am sorry to say, correct. The request for information was quite a generic one about general policies, so we assumed that the specific request for me was deliberate, and I did not know that you wanted someone who could talk about C225, and I really cannot. But I can tell you some things about the approval rates for cancer drugs and how long things take. As you undoubtedly know, we approved Gleevec in 2.4 months. The data was very good and very powerful. For any drug that is a fast-track drug, as this one apparently is, we have a response time of 6 months. We essentially always meet that goal, so that once C225 is before us, I am quite sure there will be an answer in that time or less.

Mr. BURTON. So the timeframe you are talking about in a generic way is about 6 months?

Dr. TEMPLE. Well, that is the time for response. The answer could be yes or no.

Mr. BURTON. So the data will be reviewed within 6 months?

Dr. TEMPLE. Yes. That is our goal date for any drug that receives priority—

Mr. BURTON. And then after 6 months, if there is a problem with the drug, then there is a continued reevaluation?

Dr. TEMPLE. Well, our initial response is one of three things at the present time. It is, "you're approved," and here is the label that is approved; you are "approvable" with modest amounts of additional information—the amount of information can be changes in labeling or something more important. If it is just changes in labeling, we respond to the resubmission in 2 months. If it is more, we respond within 6 months. Or it could be nonapproval because people do not believe the data are persuasive. I have no idea what the outcome on C225 will be. From what everyone says, they seem optimistic, but I cannot tell you any more than that.

Mr. BURTON. Can we make a formal request that we get that information from FDA, whoever is in charge of that, so we can take a look at that?

Dr. TEMPLE. OK. I will ask them to provide what they can. It may have to be provided to you in confidence, because those are commercial considerations, but we will certainly get you what we can.

Mr. BURTON. Well, I can understand the ramifications.

Dr. TEMPLE. Let me mention one other thing. I do not know that they are ready to do this and I do not know what we would say in response to it, but if the company wanted a treatment protocol approved, we respond to those requests within 30 days, and that has been in the rule since 1987.

Mr. BURTON. Dr. Waksal, have you requested that treatment protocol?

Dr. WAKSAL. What we are doing right now, and we have consulted with advocacy groups and talked to the FDA, we do not have yet the manufacturing capability, according to FDA guidelines, that will make enough of this drug available in a treatment protocol.

Mr. BURTON. I am not familiar with how all of this works, so I am kind of a neophyte in this area. But let us say that you had not necessarily your drug, but some drug that showed promise, and you knew that there were 130,000 people a year that were suffering from this and it had been shown to be pretty successful. Can you subcontract with a major manufacturer of pharmaceuticals to get that to the market while at the same time you are working on getting approval for your new facility?

Dr. WAKSAL. Yes, one could, and that is exactly what we have done with IMC-C225. What we did, because we knew that we had to build a larger facility and we did not want to wait, there is—now, it is a little different than from the—in the Bureau of Biologics, where we are dealing with our protein-based drug, than the group that Dr. Temple normally deals with. So each of the facilities that make our particular drug have to be licensed by the FDA for our particular drug. So we went to a group that does contract manufacturing, Lanza Biologics, to put together an agreement, where they would make our product for us under contract, and we have put together—for our approval process, we used their facility as the site that made our drug for our FDA application which we are going to put in very soon. Our own facility being completed right now will have to go through the same type of approval process, that is, that we, as we scale up and begin to make our drug in our own facility later this summer, we will go through and make three consistency lots, and then apply for that facility to be approved, and then have more drug available for these kinds of programs.

Mr. BURTON. But the contractor that you are using right now to produce the product is limited in the amount that they can produce.

Dr. WAKSAL. That is correct.

Mr. BURTON. And that is why you stopped compassionate use?

Dr. WAKSAL. That is correct. Right now, even the contract manufacturer that we are working with, has one 5,000-liter—just to give you size dimensions—one 5,000-liter fermenter committed for about 25 runs, you know, this year. Our facility that we are building has three 12,500-liter fermenters with 10,000 liters of capacity each. So we have invested a good deal of moneys to try to get enough of this drug available later so that we can make this available for all the

people that need it. And even with that, that is not going to be enough for the future, we do not think, and we will be breaking ground in the future for an even larger facility.

Mr. BURTON. How many people are in your clinical trials right now; do you know?

Dr. WAKSAL. We have treated thus far, between January 1995 and now, over 700 patients.

Mr. BURTON. 700, and you have treated 30 approximately for compassionate use.

Dr. WAKSAL. Yes, about 4 percent.

Mr. BURTON. And the capacity of the production facility is taxed with just that number?

Dr. WAKSAL. That is right. Sadly enough, we are looking at opening up new clinical trials, and I must say that the really sad thing is, for every patient that gets the drug in a compassionate fashion, patients on the clinical trials do not get the drug when we are limited by the type of drug, a protein-based drug that we are making, we are so constrained right now, that we are limiting the amount of clinical trials that we would otherwise be able to do simply because of the lack of drug.

Mr. BURTON. Is there anything that could be done—and this is a generic question—the FDA has to approve these things. And I mean, obviously, that is something that I think we all agree needs to be done. You do not want a contaminated product put in the market that is going to kill people rather than help them. But is there anything we could do to speed up the process from your producer now, and whatever company, and I do not want you to get in trouble with the FDA and have them give you a hard time because of what you are going to say. But I would like to know if there is anything that can be done to speed up the process for these new promising drugs like this one?

Dr. WAKSAL. Look, actually, we have had a very good working relationship with the FDA.

Mr. BURTON. Do not be diplomatic.

Dr. WAKSAL. No, I am not being diplomatic. I am telling that we have gotten fast-track designation. They have worked with us to try to help direct us what we need to do in our new manufacturing facility. I am sure there is lots of things that the FDA could do to speed up the process in terms of what we believe is going on, but I am sure that they are as constrained as we are in timing.

Nevertheless, we are moving forward. We believe that this product is moving forward very rapidly through the FDA approval process, and could very well be on the market sometime in the first half of next year.

Mr. BURTON. First half of next year.

Dr. WAKSAL. Yes.

Mr. BURTON. But it still will be limited because of your production facility.

Dr. WAKSAL. Well, the new facility, we hope will be up and will be going through the approval process, so that we can make enough drug available for the approval process after launch.

Mr. BURTON. I have some more questions. Mrs. Davis, do you have some questions?

Mrs. JO ANN DAVIS OF VIRGINIA. Thank you, Mr. Chairman. I guess I have one, and it relates to Mr. Baxter's son. As I heard in his testimony, his son's doctor has the drug out in, I believe, California, and I guess I am curious as—and I understand that he is 16, and that you are not allowed to give it to—I guess you could not give it to anyone under 18, but, you know, granted this is a disease that you do not expect to find in a 16-year-old. And I guess my question is, if the doctor has the drug, could you not then ask the FDA to make an exception and let you give it to this 16-year-old, whose prognosis is just a couple months? He cannot wait till the first half of next year.

Dr. WAKSAL. No. That is absolutely true. That is not the issue here. One, we will go to—we would go to the FDA, and we made it clear that we would go to the FDA to lower the age requirement, and I am sure the FDA would comply in that particular case. I do not think that is the issue here. And the issue of clinical trial sites is one, where we do these clinical trials all over the country. We have clinical trials going on in California out West, obviously. Dr. Rosenberg is one of our investigators in our head and neck trial. Unfortunately, in the colorectal study, the closest state to the Baxter family is Indiana. We have one of the clinical trials going on in Indianapolis right now. But it is very difficult to open up a new site, not knowing still whether David is a candidate yet for C225. We have no idea yet. He has not failed his conventional therapy yet, and we do not know whether he is positive for the molecule that our particular antibody attacks, the EGF receptor. So we cannot open up a site prior to knowing whether or not a patient is a candidate. So it is still unclear right now, and we do try to be as accommodating as possible in this particular situation, but again, it is a very difficult situation. You cannot open up a site for a single patient prior to knowing whether or not the patient is going to be eligible for one of those trials, and it takes a good deal of time to do just that, to open up one of these sites and to go through the approval process for those institutions.

Mrs. JO ANN DAVIS OF VIRGINIA. And I guess that brings me to the question, back to, I guess, Mr. Santino. I believe his wife was denied because she was, from his testimony, too sick or had too many treatments. And could you explain that to me so I could understand it a little better?

Dr. WAKSAL. Well, first of all at the time, unfortunately, and I feel terrible about Mrs. Santino, but we had no compassionate use protocol in place after January. We ended it because of number of patients that we had. We could not successfully deal with the list any longer. We did not really have enough drug to make it available after that. The list had gotten too long. And I am very sorry that, unfortunately, from the point of view of the Santino family, that we did not communicate that properly, and probably should have had letters sent out. Unfortunately, our medical affairs director tried to answer all of these phone calls personally, and it was not something that was acceptable to the Santino family.

But at the point in time that we design these trials, these trials have very fixed criteria, and we cannot deviate from those criteria. Those criteria are negotiated with the FDA, and once they are set, they are set, and the people that enter those trials have to fit the

age, the disease stage, and etc. All of the criteria that we negotiate with the FDA to move these drugs forward in a proper fashion so that the clinical community and the FDA can assess whether or not these drugs are going to be useful to the population at large, to the clinical population that we are talking about.

So, in effect, sometimes patients are too sick to get on one of these trials, because their health does play a role in all of these things, and obviously, that is who we are dealing with, sick patients, but the clinical trial protocols are so defined, that there are patients that cannot enter them.

Mrs. JO ANN DAVIS OF VIRGINIA. Thank you. And I agree with what Ms. Kellum said in her testimony. I think we all would like to find a cure to this terrible disease. It has affected my family and my husband's family. And it is just something that I wish you the best, and if there is anything you can do to help David, I would appreciate that.

Dr. WAKSAL. We are trying.

Mrs. JO ANN DAVIS OF VIRGINIA. Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Mrs. Davis.

How do you determine if someone is positive for the EGF?

Dr. WAKSAL. There is a test that is done that is a pathological test, where we utilize a marker that sort of lights up the molecule if it is there, and then the pathologist can say that the patient's tumor is either positive for this receptor or not.

Mr. BURTON. OK. We have had a number of cases in my family, one that is current. And I have been in a lot of facilities where they administer chemotherapy on a regular basis. And a lot of people who get chemotherapy, their immune systems are depressed while the tumors are being killed hopefully. And I just wondered, if people go through a complete series of chemotherapy treatments, does it make them more likely to be able to take C225 or less likely?

Dr. WAKSAL. Well, our drug—

Mr. BURTON. Does it depress their immune system to such a degree that they would not qualify?

Dr. WAKSAL. No. And if—

Mr. BURTON. Or can you give me a comparison, those who—and I do not know if you have this kind of information—those who have taken C225 without chemotherapy being first administered, and those who have had it administered?

Dr. WAKSAL. Well, some of the first studies that we have done are obviously in patients that have become refractory to chemotherapy, that no longer respond to their chemotherapy. And then they get to IMC-C225 in combination with the therapeutic agent that they failed. So the earliest responses we have seen have been in patient populations that have already failed all the existing and approved chemotherapeutic agents. We have data, earlier data that suggests that in patients that have not necessarily failed but are more stable disease patients, that we may even have a better response. And the whole purpose of—

Mr. BURTON. Do I interpret that to mean that those who may not have had chemotherapy?

Dr. WAKSAL. Well, those who are not failing chemotherapy, but are taking the chemo and the chemo is having some effect. In those patients there may even be a better response, and in fact, that is

our approach to this whole process of getting approval. We are first applying for approval on the phase II data using the fast-track designation that Dr. Temple talked about for cancer drugs, but it is provisional, sort of conditional approval. And the next thing that we are going to be doing and that we are opening up right away is an earlier stage study, a very large clinical trial in patients who have never received chemotherapy and who have just been newly diagnosed with these types of tumors with colorectal cancer.

Mr. BURTON. So you are starting a new study right now on people who have not taken chemotherapy, but—

Dr. WAKSAL. Who are chemo-naïve, that is correct.

Mr. BURTON. To see if C225 is more effective or less effective. I see, OK.

Let me ask Dr. Temple or Ms. Delaney. Ms. Delaney, we have not been able to get you to answer any questions. But one of the things that I think that Mrs. Davis, Representative Davis talked about and the people of the first panel talked about, was the lack of answers, the lack of communication. What can FDA do in conjunction with these manufacturers of new drugs to get this information on the Internet so that people can find it? And if they do not have—if they are not Internet literate or computer literate, as many people are not in this country, how they can get a hold of this information by contacting the FDA. I know that you have a lot to do over there, but it seems to me that one of the most hopeless things people go through is seeing a loved one or themselves being in this situation, and they say, “What is available? What can we try? What can we do to save their life?” And they cannot find the answers. I mean, that has got to just drive them up a wall, especially if after the fact, after somebody dies, or they are so depressed and their immune system is so depressed that they cannot survive, they find out there was something out there and they could not find it. And we had a couple of people on the panel before you that mentioned that.

So what can FDA do in conjunction with the private sector to make sure all that knowledge is accessible?

Ms. DELANEY. Well, actually, the scenario that you just presented, Mr. Chairman, is pretty much the standard phone call that we get to our office every day. And it is people who are pretty much out of options, or many people believe once they are diagnosed they are out of options. They are very confused and upset by what has happened.

In cases like that, when it is a first diagnosis, we recommend that people first of all talk to their doctor. Second of all, that there are many, many cancer patient advocacy groups that are out there to help them, and we have a huge resource list. But the National Cancer Institute is really—there is a huge educational arm to the Cancer Institute, and the best place for people to find out information about new drugs in development in their cancer is the Clinical Trial Registry. It is known by its acronym of PDQ, but it is available through [clinicaltrials.gov](http://clinicaltrials.gov), and—

Mr. BURTON. Excuse me. I cannot remember which gentleman it was. I believe you said that you had four Internet sites yourself?

Mr. SANTINO. Well, the—

Mr. BURTON. I know, but you are obviously Internet literate.

Mr. SANTINO. I do. I have four myself.

Mr. BURTON. You have four yourself. And you went through everything time and again, and you could not find information that should have been readily available. I think that is what your testimony was.

Mr. SANTINO. What is available it is not on the Web site anyway.

Mr. BURTON. It is not on the Web site.

Ms. DELANEY. But that is just for people that are first diagnosed, and clearly, Ruth-Ann Santino had been through all the standard treatment.

And so when we get a call or people want to know about a drug, and they have exercised all of their options with the standard treatments, we then try to assist them in finding the different places where they might look for drugs. There are Web sites, that—actually, when I talked to Ruth-Ann, the Web site we told her about, which she did not know about prior to that phone call, was pharma.org, and that is the Pharmaceutical Research and Manufacturer's Association Web site. They do a publication every other year in cancer called "New Drugs in Development in Cancer." There are 402 drugs listed by tumor type, and it is available on the Internet, and you can search it in a PDF file very easily.

Mr. BURTON. Let me ask you this question. You indicated that after they have gone through their conventional treatment, what if they do not want to go through what is called conventional treatment? What if they have an aversion to, say, chemotherapy?

We have a young man, the Thomas Navarros case. I am sure you are familiar with that. It has been all over the media. And he was denied access to experimental treatment because he had not first failed what the FDA said was a standard form of care, chemotherapy and radiation. Why is that and can people get information if they do not want to take chemotherapy and radiation because they think there is a—

Ms. DELANEY. I am going to let Dr. Temple answer that question, but I wanted to—can I tell you about what we do with companies to make sure on this compassionate use, before he answers that question? Would that be OK?

Mr. BURTON. Sure, sure, sure.

Ms. DELANEY. When it is clear that there is a number of phone calls that are coming in on a new drug—for example, this happened with C225 and a number of others in the last 2 years—we then place a call to the company, and we say, Look, I am sure you are getting many more calls than we are getting. The National Cancer Institute is also. We need to sit down and talk about what is your policy? Do you have one? If you do not have one, please develop one, and we will help you sit down with the patient advocacy community and make that policy clear to them, so that a phone call to the Colon Cancer Alliance is the same thing as a phone call to the National Cancer Institute or a phone call to ImClone. So that a patient or family member is not having to call all these different places, that everybody knows that, for example C225 will not be available. I think Fred Santino said it eloquently. It wastes too much time.

And so what we have done, not only with ImClone, but we also have done it with a number of other companies, is to bring every-



body together. So we are sort of the convener. We do not have a lot of authority in this area. It is an initiative if you will. But we convene the groups, and I think Dr. Waksal could talk about what we did specifically with their company.

Now, I will let you speak to Dr. Temple on the Navarro case.

Mr. BURTON. It sounds like, from the first panel and from other people I have talked to, that they have difficulty in finding all this information, and if the FDA and HHS could look into that to see if there is some way to streamline the process so that on the Internet and through mail if necessary or faxes, that people can get as much information as quickly as possible might help a lot.

Dr. Temple.

Dr. TEMPLE. It may be those very sites ought to link to each other somewhat better than they do, for example. We can look into that.

The cases we have been talking about are all ones in which someone wants to use a treatment that is under investigation outside of a clinical trial. I would say, as I said before, our usual answer to those requests is yes. Sometimes these are individual cases that come to us, and sometimes investigators have a program of making drugs available for such uses.

The one case where we are inclined to say no is when there is an existing therapy that is surely lifesaving and possibly even if it is clearly life-prolonging. And in the cases that you are talking about, we thought that people were going to be denied therapy that had significant cure potential. Those are the only two cases, where, to my best knowledge, we have denied them.

Mr. BURTON. Well, I do not want get into a debate about that.

Dr. TEMPLE. I realize there was a debate about that.

Mr. BURTON. Yes, a big debate. But anyhow, go ahead.

Dr. TEMPLE. Right. But I understand there can be differences of view about whether the toxicity is worth it and a variety of other questions. But that is the one case where we have trouble.

If one—I am not going to talk about C225, but if we were looking at someone who wanted to use a drug for colorectal cancer that had not been well studied but looked promising, we would certainly ask whether the person had already received fluorouracil-leucovorin and CPT-11, two treatments that are known to improve survival. So we would think, at least initially, that it would not be sensible not to use those first. Now that could be——

Mr. BURTON. Would you deny them access then to the new experimental drug? Because Dr. Waksal said a while ago they are going to start a new clinical trial on people that did not take chemotherapy.

Dr. TEMPLE. Yes. We are enthusiastic about the trial. And he also did not say that it was being combined with chemotherapy in that case, which it is.

Mr. BURTON. It is going to be combined with chemotherapy?

Dr. WAKSAL. Yes, it is.

Dr. TEMPLE. Yes, that would be the usual thing to do. You do not——

Mr. BURTON. What if the patient does not want chemotherapy, they cannot get into the clinical trial, they cannot take that C225?

Dr. TEMPLE. I think that our first responsibility is to get the drug approved, they patients then and physicians can make available the drug to those patients who do not want chemotherapy. But this drug works best, like other anticancer agents, in combination therapies, and when we see it being used in combination with radiation or in combination with other antineoplastic agents, we really get the most dramatic types of responses.

Mr. BURTON. I see Dr. Weldon has joined us. Did you have any more comment before we yield to Dr. Weldon? Dr. Weldon, do you have any questions?

Dr. WELDON. Yes, I do, and I want to thank you, Mr. Chairman, for calling this hearing. I was unfortunately tied up in another committee on some space policy issues, which as you know, is very important for the District that I am in.

But this—I have been—it is kind of been there and done that. I have seen these cases where you have patients with a problem that could possibly benefit from a clinical trial drug and does not meet the qualifications for the clinical trial for a variety of reasons and is denied. And do we need to seriously look at—maybe I will ask you, Dr. Temple. You are with FDA, I understand.

Dr. TEMPLE. Right.

Dr. WELDON. I would imagine FDA is coming under increasing pressure, and NIH, on this issue, as the proliferation of the Internet and the health care consumers, cancer patients getting much more knowledgeable of what trials are out there and what drugs are available. Now today, that Internet is so amazing, anybody could sit down in their living room, particularly if you have a high-speed access, and you can just get incredibly well educated. Literally, what you used to have to hire staff or professionals to research for you, poring through libraries, you can access in minutes. And do we need to consider changing policies either at the administrative level or the law, to allow more compassionate use of these compounds?

Dr. TEMPLE. Well, far be it from me to comment on whether you need a new law without direction from the Department, but our current policies are very permissive on those matters, as my testimony says. Once a drug looks interesting and promising, there are many ways to make it widely available if a sponsor wants to. But as Dr. Waksal has pointed out, there may be impediments to that, availability of the drug, dilution of their own resources.

And also you could ask about doing it fairly. Any individual case of a person who has failed other therapy is obviously evocative, as we have all heard, and quite terrible in many ways.

The question though that comes further is, if you took all people who had failed the available therapy for colorectal cancer, which unfortunately is most people with metastatic colorectal cancer, do we have enough information to make the drug available to all of them even before the studies are well along? That is a difficult question. I am not trying to tell you what the answer is, but we have a system that says that there is supposed to be a certain amount of evidence before you essentially make the drug available to the whole population. That is a difficult question.

I actually think that is less of a problem than one might wonder whether it would be, because the number of drugs that sort of look

exciting like that at any given time is modest. That is unfortunate in some sense, because you would like to have more of them. But for the few drugs that are getting people very excited at the oncology meetings, I believe the system can cope with them, but people have to be willing and able, and as Dr. Waksal just said, they were not able. They did not have the drug.

Again, I cannot speak for the particular case, but this is a drug where an application is imminent or with us? An application is imminent. They finished phase 3 studies, and there appear to be responses. The definition of what is acceptable for a treatment protocol or a treatment IND it has finished all its trials and looks promising in the trials, and treats something that has no other treatment. Well, people who have exhausted standard therapy for colorectal cancer have no other treatment, so it could very well meet the requirements for treatment IND. Again, I am not trying to speak for the Center for Biologics.

But those mechanisms are available to be used. It is not that the criteria are onerous or anything like that. In fact, you are even allowed to sell the drug.

Dr. WELDON. So these stories that get in the press, they are the exception?

Dr. TEMPLE. Well, again, I am not going to say that because I cannot say I know the entire experience. I am sure there are people who are frustrated by the fact that they have exhausted available therapy and have nothing to seek. Well, sometimes that is because there is not anything reasonably well developed to seek. But where there is, where, as I said, it is sort of exciting people at ASCO, whether it is Gleevec, it is C225, there are mechanisms to make those drugs widely available, and we encourage them to be widely available. There is no reticence on FDA's part; there really never has been.

And such arrangements do exist, but, you know, distributing the drug to 10,000 people one-by-one, investigator-by-investigator, is a lot of work for a drug company. They may or may not want to do it, and they want to devote their resources to gaining approval and making the drug available to everybody. It is a complex judgment. I would not want to have to make it for them.

Ms. DELANEY. May I add to that? From the cancer patient advocacy community perspective, this whole issue—and I think in other disease areas as well—there is unanimity of agreement, that a much broader public discussion needs to be had because there are so many questions that are—some are beyond our agency's authority. The ethical issues that are involved here, disease by disease differences. I mean, it is interesting to see. In the advocacy community, the positions are more rigid in opposition to compassionate use in the disease areas where there are a lot of treatment options. But in the disease areas where there are fewer treatment options, they have much more liberal views about this. And so it is something that, you know, that a lot of the advocates feel needs a much, much larger discussion that would involve the government, the industry, and the patient advocacy community in many disease.

Dr. WELDON. Thank you, Mr. Chairman.

Mr. BURTON. Thank you.

Mrs. Davis, you have any more questions right now?

I have a few more questions. It is going to take a little bit of time. In other countries, there is different therapies and treatments that are being utilized today that have not yet been approved by the Food and Drug Administration in this country. Many patients are going to other countries because they want to try these other therapies which have not been approved by our health agencies.

Do you share any information or talk to these other countries like Germany or other countries where they are providing treatments which have—some of them have some pretty good track records because we checked into those? Do you talk to them? Do your health experts at FDA and HHS communicate with them at all?

Dr. TEMPLE. We do not necessarily talk to them about a specific drug that is available. What triggers our interest generally is an application from a company to market a drug or to study it. If there are drugs that are very promising that are not even under study in the United States, I am not aware of any. We are aware of some drugs that are marketed elsewhere that have for one reason or another not been approved. And we are committed, actually, to encouraging a manufacturer of any drug that looks promising abroad and that is not here, to come in. We have only a limited capacity to be encouraging. Nobody has to come to us if they do not want to, but in the cancer program we outlined some years ago, we made a commitment to do that. And we have not found very many that we are not aware of or that are not at least under study here. But, you know, you may have found some we do not know about.

Mr. BURTON. You serve as adviser to the National Center for Complementary and Alternative Medicine, do you not?

Dr. TEMPLE. I am one of our representatives, right.

Mr. BURTON. How much involvement have you had with offering advice on research to them?

Dr. TEMPLE. Well, when people want to study an alternative therapy and submit an IND to us, which we encourage them to do, we definitely give advice on how to do the trials and how to make them optimal. I can give one example. It is outside the oncology area. When the NIMH, in conjunction with NCCAM, wanted to study St. John's Wort for depression, they came to us with a trial, and they were going to do a direct comparison of St. John's Wort and placebo. We advised them that they ought to include an active control standard agent as a treatment also because we knew that many trials of good design cannot tell active drugs from placebo. So they are doing a three-arm trial that will give a much more definitive answer than the recent trial that compared St. John's Wort with only placebo. So we try to give the best advice we can.

Mr. BURTON. Do you think patients should have the right to go completely alternative in their treatment of cancer, or should they go with a conventional treatment, chemotherapy, radiation?

Dr. TEMPLE. Well, they have the right. I mean, these things are available.

Mr. BURTON. I was asking your opinion.

Dr. TEMPLE. Oh, I think they should have the right as a sort of freedom issue, and in any event, the law allows them that right. So do I think it is wise, is a different question? But I think I will not offer a comment.

Mr. BURTON. Do you remember the young man we were talking about a little bit earlier, Thomas Navarro? His parents and he wanted to have that right, and they were denied that right and had to go through the other processes.

Dr. TEMPLE. Well, I probably misspoke. This is a drug, although it is alternative in some sense. It is a drug that is being studied for its ability to treat cancer. And it has been—its use has been allowed in hundreds of people despite not a great deal of evidence of effectiveness, and we have not tried to discourage that at all.

Mr. BURTON. Only after the traditional therapies were used.

Dr. TEMPLE. Or if there are not good therapies. There are many tumors where there are not good therapies. The cases where we have objected were where curative therapy was being denied. Again, I accept the idea that people can disagree on that, but I think our principles were fairly clear.

Mr. BURTON. There may be disagreement, but when you are the person that has the cancer of the pharynx or the husband or the wife of the person that has the cancer, it takes on a little different dimension. The former head of HHS had one view of a cancer therapy treatment when he was Governor. Then when his wife became ill with cancer, he tried all these other treatments that were not approved because he wanted to save her life. So, you know, when your ox is gored, it is a little bit different.

For instance, let us take you for instance. Are you married?

Dr. TEMPLE. Yeah.

Mr. BURTON. If you are married and conventional treatment is not helping your wife and she is going to die, would you try other things?

Dr. TEMPLE. Well, that is not the question we are talking about here. We have not hesitated to allow the treatment you are talking about in people who have exhausted other therapy.

Mr. BURTON. After they have exhausted other therapies.

Dr. TEMPLE. Well, that is what you asked me about. If my wife had something and had not responded to available therapy, would I try something else? My answer is I probably would not, but I am mulish that way, and besides, she would be the one to decide. That is how it works in my house anyway.

Mr. BURTON. Do you think an individual ought to be allowed to opt out of chemotherapy and radiation, and then go straight to treatments while they are experimental, that might be less toxic?

Dr. TEMPLE. Well, again, when that issue has arisen, where the therapy is importantly effective—this is what I am talking about—there are many cancer therapies where the effect is modest or uncertain, and we have not insisted that people try those. It is only where the available treatment was curable. In the two cases we are talking about, the cancers were curable by available therapy. That is not a very common situation in widespread cancer, unfortunately.

One was Hodgkin's disease and one was a malignant glioma. So, you know, we just could not, as physicians and as regulators, think that was reasonable.

Mr. BURTON. Have you heard of the National Foundation for Alternative Therapies?

Dr. TEMPLE. I am not sure.

Mr. BURTON. A former colleague of ours is the head of that, and I think they have examined, I think, 73 different clinics and facilities around the world that provide alternative therapies, and they found some that have some fairly great results, one in particular in Germany that has been very successful. And I guess the question I asked a while ago I would like to ask again, how do you communicate with these other clinics and other facilities around the world that may have had some success by using a different approach to dealing with things like cancer?

Dr. TEMPLE. Well, again, what triggers our interest in something is that someone wants to use it here, wants to use it under an investigational program or market it. When they do that, they bring forth the data that they think supports this use. We strongly encourage investigation of alternative methods or bringing the data and seeing whether it needs to be investigated further. We are, perhaps surprisingly, non-dogmatic about theories of cure. We are skeptical about all of them. So we like to see people bring forth the data, and alternative treatments can be studied just as regular ones can.

Mr. BURTON. But there is no outreach program. I mean, you wait till they come to you with alternative or complementary or new therapies or new—there is no program by FDA to reach out to other facilities and other governments around the world that may have tried a different approach that has been successful. And I guess my question is: why is that? It seems to me that that might be a resource that our health agencies haven't been tapping. Why would you not talk to the people over in Germany, or England, or France or other countries, Spain, where they have had some very positive results with other therapies? Why do you wait until they come to the United States and have to go through the bureaucracy of the FDA?

Dr. TEMPLE. Well, our bureaucracy with respect to studying things is de minimis. It is very easy to get into clinical trials, and someone has to want to do that.

Mr. BURTON. I understand, but they have been in this clinical trial mode since 1995. We are 6 years later. Hundreds of thousands of people have died from colon cancer probably during that time period. If there is a facility in Germany or someplace else that has had some success with that, why isn't there an outreach program that would eliminate a six or 7-year delay while clinical trials are going on? Why would we not at least try to find out about it?

Dr. TEMPLE. I am not following that. This is how long it has taken to develop C225.

Mr. BURTON. He said that they started the clinical trials, did you not say, in 1995?

Dr. WAKSAL. That is correct.

Mr. BURTON. OK. 1995. It is 6 years. It takes a long time for a drug to be improved even if the efficacy of it is proven. It takes a while. It takes about 5 or 6 years. And so what I am—

Dr. TEMPLE. Wait, wait, wait. We have got to be sure we are talking about the same thing.

Mr. BURTON. Well, it takes that long—

Dr. TEMPLE. No. They have been developing the data. They have only treated 700 people in those 6 years. That is how long it has

taken them to get data on 700 people. The approval process, once they submit the data to us, nowadays for a drug that is so-called fast-tracked or priority review, is something like 6 or 7 months. I know that for people who are impatient and waiting, even that is long, but it is not 5 years. The time it takes is to develop the data, and nobody knows how to do that much faster than it gets done now. You have to accumulate patients, and you have to start small and get larger and so on, so that is what we do.

I have to say, if there are curative treatments for colorectal cancer out there, and somebody is hiding them in a clinic, that would be a really strange thing. I mean, it is a dreadful disease—

Mr. BURTON. No. I am not saying they are hiding in a clinic, but they have had some success—

Dr. TEMPLE. Well, how would we not know that? I mean, there must be publications or something. Where is this drug? What could it be that is curing colorectal cancer and nobody knows about it? I am skeptical of the existence of those things.

Mr. BURTON. But there is no communication outreach program from FDA to other governments and other facilities around the world.

Dr. TEMPLE. We are trying to encourage study of any drug that is marketed in other countries for cancer. We are interested in them and have explored how to get it studied. And there are a few drugs that are approved abroad that are under study.

Mr. BURTON. I am not necessarily just talking about drugs. I am talking about alternative approaches to—in a yes or no answer, there really is no outreach or communication program with other countries and other health—and their health agencies?

Dr. TEMPLE. Well, the answer is no on that question. The other health agencies do not approve alternative medicines in the same way as they approve drugs. It is a different system. They do make botanicals available in Germany in a fairly well characterized way, but it is not the drug regulatory authority that does that. It is a different group.

Mr. BURTON. I know. I guess we are splitting hairs here. The question is if they have a success rate, it seems to me it would be something that our health agencies would at least take a look at to see if it could be applicable to people here in the United States.

Let me just ask a couple more questions, then I should be—do you have any questions? I do not want to monopolize this.

We have been told that companies are owned—sir?

Dr. WELDON. Sorry to interrupt. I did have a sort of a followup to what you were getting into before.

Mr. BURTON. Sure, go ahead.

Dr. WELDON. I have a little bit of experience in this arena, but just for the record—and maybe Dr. Waksal can talk about this—and you alluded to it, Dr. Temple. The time it takes to accumulate the data. You know, I worked on a drug for ovarian cancer when I was in medical school, and maybe you can just elaborate on this a little bit. It is not like you can just go to Wal-Mart and accumulate patients.

Dr. WAKSAL. No, you are absolutely correct. We started our clinical trials in January 1995, and first had to show, both for ourselves and the FDA, that the drug was safe by itself, and we had a small

cohort of patients that we treated to show safety and see if there was any hint of biologic efficacy, whether the drug was working at all. And as we went forward, we saw that the drug was safe eventually, and we began to use it in a number of different situations, in combination with almost every chemotherapeutic agent out there and in combination with radiation. And over—

Dr. WELDON. If I can interrupt you, you could not use the drug unless somebody failed other treatments, correct? You could not just—

Dr. WAKSAL. That was not the case, actually. First we went into patients that had failed prior therapies. But then we put together trials, for example, in patients that had local, regional—that were receiving radiation for local, regional disease with head and neck cancer, that were not surgical candidates, but had not had metastatic spread of that disease. And we used it in combination with radiation in that patient population before we went off into phase III studies, to prove statistically that our drug worked in combination better than radiation alone. And we are doing that. And that trial is moving along.

Dr. WELDON. So you have to accumulate a large enough statistic sample and you have to have controls and it just takes time for those patients to come into the system.

Dr. WAKSAL. Absolutely. I mean, one of the things that we have done, and it is because of the FDA guidelines on unmet medical needs, is in the colorectal study, we really were not using our drug in colorectal cancer initially, and it was actually because of the compassionate use situation with Shannon Kellum and her physician that we learned that our drug had activity, significant activity in colorectal cancer. We then began a clinical study to see whether or not in a patient population that ended up being about 139 patients, whether or not in that patient population, where we could ascertain in statistically significant fashion that this drug was working. We began that trial last February. We completed enrollment in that trial at the end of last July. We closed the sort of statistical timeframe at the end of January, and we are going to be imminently filing for approval for that particular indication. So that is the period of time that it has taken for this particular indication to go through the process from enrollment to completion of the clinical package. We presented that data at the cancer meetings in May. We are about to file and begin the biologics application process with the FDA, and hope that it will be one that will be rather expeditious.

Ms. DELANEY. May I just say something about—you are talking about recruitment, at least alluding to it. And while it was not particularly an issue with C225, the cancer patient advocacy community is deeply concerned about the issue of adult recruitment to cancer clinical trials. The statistics that is used most often is between 3 and 5 percent of adult cancer patients end up in a trial. In pediatric cancer, that number is roughly 70 percent. It is at least 70 percent. And many believe that is the reason that we have the breakthroughs that we have had in the childhood cancers. This is a subject that has been studied a lot, about why recruitment is so difficult. And a lot of studies have been done on it, and there are a list of reasons, but it is a very difficult problem.



Dr. WELDON. You wanted to add something?

Dr. TEMPLE. Yes. There is a quirk in the system that tends to get people late in disease studied sooner than people early in disease. Some years ago, actually, Dr. Waksal referred to this, we made it clear that we were prepared to approve drugs for refractory patients, people who have exhausted other options, on the basis of tumor response alone, that is, shrinking the tumor. Now, tumor response is a surrogate end point that suggests a reasonable likelihood of patient benefit, but it really does not demonstrate it. It is, however, much easier to demonstrate an effect on tumor size than it is to show that you have actually improved survival.

Dr. WELDON. So you are talking about you doing a scan or an ultrasound, some measure—

Dr. TEMPLE. Yeah, right. Shrink the tumor by 50 percent.

Dr. WELDON. Shrinkage, no demonstration of, per se, improved survival or clinical improvement.

Dr. TEMPLE. Right.

Dr. WELDON. Just purely in imaging.

Dr. TEMPLE. Right. In contrast for approval as initial therapy for, say, colorectal cancer, we would ask that people show that there is improved survival or improved symptomatic benefit or something like that. It is much harder to do those studies. They take longer, so they are generally left for later. It is not that people ignore that population, and it is not that if the drug were available, someone could not use the drug in that population also, but the quickest route to approval is through treatment of refractory patients. You could also say they are the most needy in some sense too. So I am not arguing that is irrational or unreasonable, what we do, but that is partly why it happens.

Dr. WAKSAL. And that is exactly the approach we have taken, first to look at that population of unmet medical need, and now moving forward into first line of therapy, and going to be initiating a much larger clinical study sowing survival benefit.

Dr. TEMPLE. But if they had wanted to make their first trial standard therapy plus—not their first trial, but their first clinical trial—standard therapy plus or minus C225, in the control trial, I do not want to speak for biologics, but in a drug setting, we would not object to that. It is OK. But that is a much harder trial to do.

Dr. WELDON. Ms. Delaney, I just want to get back to the issue you were talking about, the pediatric cases. Could it be that the vast majority of pediatric oncology cases end up at pediatric teaching hospitals?

Ms. DELANEY. Yes.

Dr. WELDON. Versus adult cancers treated at the community hospital level?

Ms. DELANEY. Well, the pediatric oncology community was real smart back in the 1960's. They all got together. They said, "Look, you know, we only represent a small percentage of the cases, like there are 10,000 cases of pediatric cancer in this country out of 1.2 million this year." So if you have got that many, you know, at St. Luke's you have got four kids with leukemia and then you have three with Hodgkin's disease out here, you know how are we going to get—so that pediatric oncology community got together and they formed a cooperative group, and they started—

Dr. WELDON. Nationwide?

Ms. DELANEY. Yes. And they started pretty much every kid on a trial, which has resulted in huge breakthroughs in Hodgkin's disease, in leukemias. You know, not necessarily cures, but way up in the high percentages of survival with metastatic disease.

What the adult cancer advocacy community wants to do is achieve those same kinds of cooperations to improve recruitment. I remember reading—I wish I could get the citation. I cannot find it again, but after animal studies, the most time consuming aspect of cancer drug development is the recruitment to the phase 3 trial. I mean, a drug like C225 is very unusual in the amount of publicity that it has gotten and the attention. So, no, it is not hard to recruit to a trial like that. But there are some other promising drugs out there that nobody knows about, that are struggling to try to get patients to the trial, and also National Cancer Institute trials, which are new combinations of already approved treatments that deserve attention. So it is something that the advocacy community is very focused on, that we spend a lot of time in our office with them on, and with the pharmaceutical industry.

Dr. WELDON. Thank you, Mr. Chairman.

Mr. BURTON. Did you have any more questions, Mrs. Davis?

Mrs. JO ANN DAVIS OF VIRGINIA. I guess something Ms. Delaney just said struck a chord. You said there is a lot of drugs out there that would love to have recruitment. But wasn't that the very thing that we were asking the question, how do these people know that there are drugs out there? I mean, we are going back to the same thing. You know if you had cancer and knew that there was an experimental drug out there, you would certainly want to be recruited I would think.

Ms. DELANEY. Well, one of the ways is for the pharmaceutical industry to place their drug trials in a public access data base and that is one of the FDAMA laws or rules, section 113, is that once a drug reaches the point of looking into efficacy, that drug, in life threatening diseases, needs to be added to a public access data base. And right now in the National Cancer Institute's data base there are about 1,835 clinical trials. Only—well, really, the number right now is exactly 184, are from the pharmaceutical industry. We know that here—you know, just abstractly, that there are many, many more drug trials out there in cancer than that. So we need to have better cooperation. We are working with them. There is a draft guidance out for the pharmaceutical industry to use, but we need to have more of their input—that is how people will learn about what those drugs are, what trials are out there, is if there is better cooperation with making the information available at least at phase 3.

Mr. BURTON. Would you yield to me just a minute? FDA has all kinds of regulatory authority. Why cannot you just tell or pass a regulation over there, which you do quite frequently, and say that the pharmaceutical companies have to do that so that the information is available through FDA to be able to be put on the Internet? I mean, why say, well, they are out there and they are not telling us all that stuff. Why don't you just say that they have to do that.

Ms. DELANEY. Well, there is a draft guidance and it is process that is—

Mr. BURTON. Wait a minute. It is a draft guidance and it is in what process?

Ms. DELANEY. There is a process, and a draft guidance has been developed, and you know, we have received responses from industry, and it is incorporated. But in the meantime, the advocacy community—and I am not speaking for FDA right now—the advocacy community has been asking them to cooperate, and it has been difficult.

Mr. BURTON. Who has been asking—you have been asking the pharmaceutical companies to cooperate?

Ms. DELANEY. Yes.

Dr. TEMPLE. Well, why doesn't FDA tell them to cooperate? Well, actually, you told them to. FDAMA has a clear obligation for them to do it.

Mr. BURTON. Well, if they were told to do it, why are they not? Are they violating the law?

Dr. TEMPLE. I do not fully know the answer to that. We will find out what the difficulties are. I cannot tell you off the top of my head.

Mr. BURTON. Well, the information is extremely important, and I think the gentlelady asks a very important question. If that is out there, and there is new therapies and new processes that can be utilized to help people fight cancer, it is almost criminal not to let all that information be put on the Internet, or in some way to communicate.

Do you have any other questions?

Mrs. JO ANN DAVIS OF VIRGINIA. Well, I just wonder, are we not letting the oncology doctors know about it, so that they can give the information to their patients?

Dr. TEMPLE. My experience is most oncologists, especially at good centers, are very aware of the latest drugs that look exciting, but if something is below that level, they may not. I think we have to find out why not as many things are getting on that site as we think should, and I do not know the answer. We will look into it.

Mrs. JO ANN DAVIS OF VIRGINIA. Thank you.

Mr. BURTON. We will be following up on this, I promise you. We will followup on it, we will make sure, and I want to thank you gentlemen for being here to tell us your stories.

I have two more questions quickly, and then what I would like to do is submit to you questions for the record because I do not want to keep you here past midnight, so if you would accede to our wish to answer some questions we submit to you in writing, we will not ask you all those questions now.

And, Dr. Waksal, I appreciate very much your candidness with us today, your candor. You have been very helpful. And I just wish that there was more ability for you to produce more of your product so that people could use it for compassionate use. I just—it seems like to me if it is that effective, it is just a shame that you are not in that mode yet. But we appreciate your candor.

Dr. WAKSAL. We are working as hard as we can to take care of that situation.

Mr. BURTON. Well, good. Two questions. We have received a number of complaints from families, who when reviewing cancer research papers, are dismayed that researchers report patients as

successes from the treatment even when the patient dies. How can families be secure that a treatment offers hope when reducing a tumor is more important than keeping a patient alive in research? I mean if the patient dies, how can it be a positive in the research?

Dr. TEMPLE. Well, there is a difficult and unpleasant reality in the treatment of solid tumors that are metastatic, and that is that cures are extremely rare, even for drugs we consider promising. The standard therapy, initial therapy for colorectal cancer is fluorouracil-leucovorin. Now you add a drug called CPT-11.

Mr. BURTON. Chemotherapy.

Dr. TEMPLE. Chemotherapy. Surgery, if you can get the tumor out, those are sometimes cures, and that is fine. But if the tumor metastatic, and if it is not removed by the surgery, mortality is almost universal.

Mr. BURTON. In what timeframe?

Dr. TEMPLE. Oh, that varies very much depending on the tumor. It could be 12 months for some as an average, and it could be 3 years for others. Breast cancer is famous for being much longer. Success is—it depends on how the study defined it. Success may mean they shrank the tumor by 50 percent for a period of a certain number of months. Now, you might not think that is very important if the person then goes on to die at 6 months, and I would not disagree with you, but it is a proper measure of tumor activity. One of the things we have learned in other parts of oncology in the treatment of leukemias and things like that is sometimes you can find one drug that does a little something, another drug that does a little more, and put them together and you start to see responses that are better than you would have predicted from the others, and that is what everybody is dreaming about.

But so far the treatment of metastatic solid cancers, except for some odd things like testicular, is grim.

Mr. BURTON. You know, it seems to me that there ought to be a way to clarify that when you do your statistical analysis. I mean if a person is judged to be cured for a cancer and they die in 6 months—

Dr. TEMPLE. They are not judged as cured.

Mr. BURTON. Well, whatever the—

Dr. TEMPLE. Well, the usual endpoint in a cancer trial that is looking at mortality is whether you have delayed death. That is the endpoint.

Mr. BURTON. Well, then should it not be more clearly defined and clarified?

Dr. TEMPLE. I would have to see the things that people are upset about, but—

Mr. BURTON. The reason I say that is because people base their decisionmaking process on what kind of treatment to get for themselves and their families based upon the statistical data that you give them, and that is given by FDA to the doctors. You know, because doctors all the time quote, well, 50 percent of these people live 5 years and 60 percent live this long, and that statistical data is very, very important and it should be very clear and accurate.

Dr. TEMPLE. Well, I completely agree. The usual measure in a clinical trial is—well, there is a complicated statistical analysis to determine whether there was an improvement, but the convenient

number one gives is median survival. That is how long the average patient lived. You look at how long the average patient who did get the drug lived, and you look at how long the patient who did not get the drug lived. And if you see a difference, that is an improved survival.

To the extent anybody believes that is cure, they are not understanding the data.

Mr. BURTON. Well, is that explained in the data, that the survival rate is increased by 3 months or 6 months because this drug was used?

Dr. TEMPLE. All of our labeling would have a figure of something like that, yes.

Mr. BURTON. One more question, then I will let you go, and I do appreciate your patience.

I think, Dr. Temple, you stated that doctors are generally aware of investigational drugs that might benefit their patients. But various reports suggest that fewer than 5 percent of primary care physicians have ever referred a patient to a clinical trial, and far fewer than half of the physicians associated with teaching hospitals have referred a patient to a clinical trial. In fact, a member of my staff, who wrote this question, who was in a clinical trial for a leukemia drug, did not learn about the drug he is testing, which is called Gleevec, previously called STI571. He did not learn about that from his doctor or from a government sanctioned Web site. He learned about it by an informal Web site that was established by a patient who was successfully treated in an earlier phase of the drug trials. His primary care physician knew nothing about it. His oncologist was somewhat aware of the drug, but vigorously discouraged him from applying for a clinical trial, stating, "That drug is in short supply, and they are not going to waste it on someone of your age."

In view of that, do you not agree, Dr. Temple, that a lot of work remains the help doctors become generally aware of the investigational drugs that might benefit their patients, and thus the Web site information?

Dr. TEMPLE. Yes. We are very enthusiastic about that. I think the points that have been made earlier about making sure Web sites contain these things is important. I actually do not have any belief that the average doctor necessarily knows about the latest cancer chemotherapy. I do think most oncologists do know about the more prominent and promising things. But I think for the family practitioners who may be serving a lot of people, at least initially, more information does need to be available.

Mr. BURTON. Well, let me thank you all. Any more questions? Well, first of all, thank you very much for being here. Thank you for your patience. I know it has been a long day. And Dr. Waksal, thank you very much. Thank you for being here. And we will be in touch with you for further hearings down the road. Thank you very much.

We stand adjourned.

[Whereupon, at 5:05 p.m. the committee was adjourned.]

[Additional information submitted for the hearing record follows:]

## National Organization for Rare Disorders, Inc.®

NORD • 100 Rt. 37, P.O. Box 8923 • New Fairfield, CT 06812-8923  
Tel: (203) 746-8518 • FAX: (203) 746-8481  
TDD (for hearing impaired) (203) 746-6927  
http://www.rarediseases.org • e-mail: orphan@rarediseases.org



June 27, 2001

The Honorable Dan Burton  
Chairman, Government Reform Committee  
U.S. House of Representatives  
2185 RHOB  
Washington, D.C. 20515

Dear Mr. Chairman:

The National Organization for Rare Disorders (NORD) welcomes the opportunity to submit comments to the U.S. House of Representatives Government Reform Committee regarding your hearing of June 20 on the subject of "Compassionate Use IND'S - Is the Current Process Effective?"

Access to experimental treatments is critically important to people with currently untreatable rare diseases. Since little research has been pursued on many of these conditions, they are usually treated with medications that were developed for more prevalent and well-known diseases. Therefore, clinical trials with drugs designed specifically for a rare disease offer hope to patients and families.

The *Orphan Drug Act* has been very successful in spurring development of new treatments for "orphan" diseases. We currently have more than 220 orphan drugs on the American market and more than 800 are in the research pipeline. Many orphan drugs are for rare forms of cancer. In fact, the NIH suggests that there are only five or six cancers that exceed the 200,000-population maximum that defines orphan drug criteria.

Since most orphan diseases are genetic, the awesome progress of the Human Genome Project is revealing critically important information that may point the way to possible new treatments, such as enzymes and proteins that could correct the biochemical defects in genetic diseases. Undoubtedly, many patients and parents will demand access to new experimental treatments. Understanding their desperation is just as important as understanding the careful pursuit of science, along with the history of human research tragedies that evolved into current human subject protection rules.

... continued ...

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Alpha One Antitrypsin Deficiency  
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Wilson's Disease Association

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Associations are joining continuously. For newest  
listing please contact the NORD office.  
Rev 301

Dedicated to Helping People with Orphan Diseases

First, scientists and drug companies admit that most drugs that begin human testing never make it to market because they are found to be either unsafe or ineffective. The basic tenet of medicine for more than a millennium has been "First, do no harm." It is, therefore, important to remember that access to experimental medicines, outside of controlled clinical trials, should not come too early in the testing process. In our experience, the FDA has not only allowed but also encouraged companies to apply for Treatment IND's during Phase III, the latest stage of clinical research, after some evidence of safety is in hand.

Second, the National Organization for Rare Disorders (NORD) has administered several "Early Access" programs for pharmaceutical companies that wished to allow patients outside of controlled clinical trials to have access to experimental drugs. These companies understand the predicament of so many desperate families who plead on behalf of a dying loved one for a chance of hope.

The problem is that there must be clearly defined rules around access to experimental drugs because without such rules there will be chaos. In fact, this is why the *Kefauver-Harris Amendments* to the *Food, Drug & Cosmetics Act* was passed. Thalidomide was an experimental drug in the United States, yet the manufacturer was giving it away to doctors who then gave the drug to pregnant women who ultimately had severely deformed babies. I urge you to remember those Thalidomide babies before you consider any mandatory changes to pre-approval access rules for experimental drugs. The rules are there for a reason, and manufacturers should not be allowed to distribute unapproved drugs indiscriminately.

The rules also have to be fair and equitable. There are people who feel they deserve access to a drug more than other people, and when there is a limited supply, as there often is (particularly for biological products), a company must avoid any appearance of preferential treatment. I can tell you from our experience that some patients launch organized lobbying campaigns and enlist reporters and politicians into a concerted effort to choose them over others. The pressure can be intense, which is why it is absolutely critical to define fair and firm rules that are understandable to the public.

In our "Early Access" programs, names are chosen through a random computer-generated selection. We have had people try to bribe us, threaten us, and precipitate political inquiries, but there is no way that the computer can be altered to select a specific name. When the names are selected, we freeze the

database and save it so that the FDA can replicate the selection, if needed. Those whose names are not selected are put back into the next pool of names so that they have another chance of being selected in subsequent cycles, if applicable. The manufacturer tells us how much drug is available for each selection so we know how many names the computer can choose.

In some cases the patients will apply, and if their names are selected, they must then go to a clinical site where they are evaluated for appropriate medical parameters of the study. In other cases, the physician applies on behalf of the patient, and the physician must make a judgment about the patient's medical qualifications for the experimental trial before submitting the patient's name. After a person is taking the test medicine, the data submitted by the physician is collected by a Clinical Research Organization (CRO) that communicates with the company and the FDA.

I believe that early access to experimental drugs in an orderly and scientific fashion is good for patients and for companies, **but only if there are no exceptions to the rules.** If only one person is made an exception to the rules outside of the random computerized selections, the whole system will implode. If just one patient not fitting the strict criteria of age, diagnosis, or biologic tests gets a drug because their congressman intervened or a newspaper reporter threatened negative publicity, then all the other patients would have the right to demand exceptions for themselves. Additionally, each person chosen outside of the process would be taking the drug away from another person who is equally or more deserving. This is why orderly access is important, and strict rules must be preserved.

Among NORD's "Early Access" programs, two drugs were for treatment of ALS, better known as "Lou Gehrig's disease." This is a hopeless and deadly illness, and families were desperate for these drugs. The first drug was finally approved by the FDA, but the second drug was ineffective. Yet, patients were convinced that this second, ineffective drug was their only hope. One woman actually offered to give us \$1 million if we would give it to her father. Mr. Chairman, we know what desperation means. In this regard, we want to make several points:

- 1) The FDA is the best judge of good science, but the FDA is not allowed to tell patients the status of an investigational drug, nor other data such as observed side effects, status of current patients, etc., because such information is "proprietary." One thing Congress could do is to allow the FDA to speak openly and frankly to patients when they inquire about experimental drugs. If the FDA cannot speak frankly without a manufacturer's permission, most of the information patients can obtain is usually overly optimistic because it is aimed at investors, not patients and physicians.



- 2) We plead with you not to consider compassionate use remedies for cancer and AIDS, thus omitting millions of people with other deadly diseases. Public policy should address all life-threatening diseases with no satisfactory therapies currently available. Public health policies that address health problems for elite diagnoses are unfair and morally unacceptable.
- 3) The FDA does not limit the amount of experimental drugs a company can manufacture. The company determines the amount it will make available to patients. While large companies such as Astra Zeneca have been very generous, small companies, particularly biotechnology firms, tend to limit manufacture due to financial concerns. There is no guarantee the FDA will approve a drug, and in the past, several small companies found themselves in serious financial peril with large amounts of inventory of useless drugs that were not approved for marketing.
- 4) When a company allows for compassionate use of an experimental drug and the drug does not get approved for marketing, they face the very sad dilemma of having to take patients off the drug. We administered a compassionate use program for a drug that was not approved, and it was tragic when the surviving patients were told they would no longer receive the compound and there was no other life-saving treatment available. But the test medicine was not life-saving either.
- 5) We believe the answer to your questions is a mechanism for better information and communication. It is true that patients want hope, but it is cruel to give them false hope. Manufacturers should be encouraged to provide compassionate use programs and to make their inclusion and exclusion criteria known to the public. Such programs must earn the public's trust by making no exceptions to the rules, even for an employee of the manufacturer.
- 6) Additionally, we firmly believe that all Phase III clinical trials should be listed on the government's web site: [www.clinicaltrials.gov](http://www.clinicaltrials.gov). This database was mandated by the *FDA Modernization Act*, but listing of privately funded trials is voluntary. To date, very few manufacturers have listed their trials, while all federally funded trials are mandated. The absence of privately funded trials on the government's web site means that patients remain unaware of other research options. We believe information about all Phase III clinical trials should be available to the public no matter the source of funding.

When families launch lobbying and publicity initiatives to force a company to provide access to a drug outside of the parameters of a compassionate use program (for example, if they don't have the appropriate diagnosis), they are tearing at the fabric of the orderly pursuit of science. If they succeed, there will be more dying patients beating at the company's doors for access, demanding that exceptions also be made for them. Moreover, families with the most resources are able to get a company's attention more easily than families with fewer resources. For those patients who do not have the target diagnosis, the appearance of a serious adverse event could significantly delay FDA approval of the drug for thousands of patients with the target diagnosis.

NORD is a non-profit, voluntary health organization representing an estimated 25 million Americans with more than 6,000 disorders. Under the *Orphan Drug Act of 1983*, a rare disease is defined as a health condition affecting fewer than 200,000 Americans. Most of these disorders are genetic and many are untreatable with current therapies.

Once again, thank you for allowing the National Organization for Rare Disorders to submit comments to the Government Reform Committee. We welcome the opportunity to work with you and all members of the Committee on this crucially important issue.

Sincerely,



Abbey S. Meyers  
President

Copies to: All members of Government Reform Committee  
U.S. House of Representatives